AN EPIDEMIOLOGICAL REVIEW OF THE INJECTABLE CONTRACEPTIVE, DEPO-PROVERA

Dr C Sathyamala

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Medico Friend Circle & Forum For Women's Health
India

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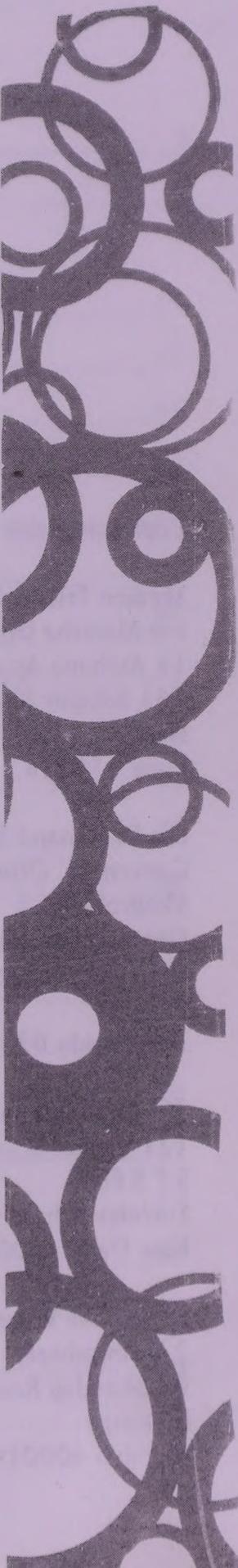products does not imply that they are endorsed or recommended.

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who have contributed their
'months' of experience

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Foreword

Injectable contraceptives are one of the areas where opinion is sharply polarised between those who are committed supporters of this technology and a strong group who equally emphatically oppose its introduction. Regardless of which category one belongs to, Dr Sathyamala's treatise should be required reading. Dr Sathyamala has carefully marshalled the facts available in the scientific literature to support her thesis that the risks consequent upon the use of present generation of injectable contraceptives are unacceptable and that these drugs should therefore not be allowed into the armamentorium available for contraception.

Those of us who believe that the risks of unwanted pregnancy far outweigh the risks associated with most contraceptive technologies, need to read this work to get a dispassionate view of the scientific evidence being marshalled against Depo-Provera and related preparations. Being better informed will enable proponents of Depo-Provera to be selective in choosing prospective users, and will empower the health care provider to better inform clients of possible consequences and side effects.

For those who are against the introduction of this technology, this work will provide a proper understanding of the reasons why some scientists say that injectable contraceptives carry an unacceptable level of risk. Too many people have opposed the introduction of the injectable contraceptives on the grounds that it removes the freedom of choice from women. It is this extreme position that has impressed many people as irrational. After all, they argue, this contraceptive technology actually empowers women to exercise choice about their reproductive behaviour.

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In essence it is not for any of us to take decisions on behalf of others. The health care provider has the responsibility to view the evidence with the greatest possible scientific vigour, advise our clients according to our best judgement but the final decision and choice must be that of the fully informed client. The decisions must be based on medical facts, not on emotion on part of the provider.

A scientific evaluation of benefits and hazards of any technology is essential to enable us to take a reasoned position on the issue. Dr Sathyamala has contributed in an important manner to our ability to decide on this contentious issue.

This is scientific work that will make it easier for many of us to get a better understanding of the subject. I would recommend it to all those interested in contraception.

Lalit M. Nath,
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Acknowledgements

I have many people to thank.

Preface

Depot-medroxyprogesterone acetate (DMPA, Depo-Provera^R) and Norethisterone enanthate (NET-EN, Noristerat^R) both injectable contraceptives, manufactured by Upjohn Co. (USA) and Schering AG (Germany) respectively, have recently been introduced into the Indian market.

The current approval of the Drugs Controller of India restricts the marketing of both Depo-Provera and Noristerat to the private sector. The marketing is also conditional on that Max India (the Indian company that is marketing Depo in India) and German Remedies (the Indian subsidiary of Schering AG) carry out postmarketing surveillance on Indian women.

These two injectable contraceptives are yet to be introduced into the government's Family Planning Programme. The Indian Council of Medical Research (ICMR) has been directed by the Drugs Controller to carry out Phase IV trials (pre-programme introduction study) with Depo-Provera. In 1984, the ICMR had completed Phase IV trials with Noristerat. On the basis of the results of Phase IV study with these two injectable contraceptives, a decision will be made to introduce one of them into the Family Planning Programme.

The Phase IV trial of ICMR is designed to look at the rate of continuation and acceptability in the general population as well as to work out the logistics of using it in the national Family Planning Programme. In all likelihood, the choice will be made in favour of Depo-Provera because of its aqueous base, less painful injections, need for fewer contacts with the health care system in a year (three monthly compared to the two monthly of Noristerat) and cost.

Depo-Provera is not a new drug. Since the sixties, it has been approved for the treatment of endometrial and renal cancer. In 1967,

the Upjohn Co. submitted a New Drug Application to the United States Food and Drug Administration (USFDA) for its approval as a contraceptive. Due to adverse toxicological effects seen in animals, the USFDA denied approval to Depo-Provera as a contraceptive. These animal studies had suggested a potential carcinogenic effect of the drug. It was only in October 1992, after the publication of the World Health Organization's collaborative multinational study on Depo-Provera and cancer (WHO,1991) that the USFDA granted approval for its use as a contraceptive. The approval by the Indian Drugs Control Authority in 1994 is very much linked to the decision of the USFDA.

With the approval by the USFDA, it appears as though the last word has been said on the safety of Depo-Provera as a contraceptive. It is our contention that considerations other than safety have led to the approval of this contraceptive. We hope this review will reopen the debate about the advisability of subjecting large numbers of women to Depo-Provera.

In India, unlike in the West, the carcinogenic potential of Depo-Provera, although an important consideration, is not the central argument to oppose its introduction as a contraceptive. In the Indian context, there are in fact more serious limitations to its use. These limitations would apply to women in other developing countries as well as to low income and disadvantaged women from the developed countries.

This monograph will examine the safety aspects of Depo-Provera. In scientific papers, the general practice is to mention a drug by its generic name. However, an exception will be made here. The contraceptive Depot-medroxyprogesterone acetate is being marketed and is widely known by its brand name: Depo-Provera. Hence in this review, the better known trade name will be used.

"DEPO-PROVERA®

Contraceptive Injection

(Sterile medroxyprogesterone acetate suspension, USP)

Patients should be counseled that this product does not protect against HIV infection (AIDS) and other sexually transmitted diseases.

DESCRIPTION

DEPO-PROVERA Contraceptive injection contains medroxyprogesterone acetate, a derivative of progesterone, as its active ingredient. Medroxyprogesterone acetate is active by the parenteral and oral routes of administration.

DEPO-PROVERA Contraceptive injection for intramuscular (IM) injection is available in 150 mg/mL vials each containing 1 mL of medroxyprogesterone acetate sterile aqueous suspension.

CLINICAL PHARMACOLOGY

DEPO-PROVERA Contraceptive Injection (medroxyprogesterone acetate) when administered at the recommended dose to women every 3 months, inhibits the secretion of gonadotropins which, in turn, prevents follicular maturation and ovulation and results in endometrial thinning. These actions produce its contraceptive effect.

The effect of hepatic and/or renal disease on the pharmacokinetics of DEPO-PROVERA Contraceptive Injection is unknown.

INDICATIONS AND USAGE

DEPO-PROVERA Contraceptive Injection is indicated only for the prevention of pregnancy. It is a long-term injectable contraceptive in women when administered at 3-month intervals. Dosage does not need to be adjusted to body weight."

(Excerpts from drug literature,
The Upjohn Company, Kalamazoo, MI 49001, USA.
Revised November 1993)

"In preventing pregnancy, both DMPA and NET-EN act essentially by:

—inhibiting ovulation;

—increasing the viscosity of the cervical secretions, thus forming a barrier to spermatozoa (and to many bacteria);

—changing the rate of ovum transport through the fallopian tubes;

—making the endometrium less suitable for implantation."

(WHO, 1990: 2-3)

1. Worldwide Prevalence of Use

(Depo-Provera) "was introduced in 1967 and is the world's most widely used, most widely available and the largest used preparation of its kind.... has been successfully used by over 30 million women in over 90 countries".

<div align="right">(Mudra Diversified[1], 1994)</div>

In the 27 years of use, 30 million women in over 90 countries is not a large number. In the 90 countries that had approved Depo-Provera for contraceptive use before the USFDA ruling, the percentage of married women of reproductive age using injectable contraceptives varied between < 0.5 to 8 (Liskin *et al.*, 1987). Indonesia, Thailand, Honduras and Jamaica were the four countries where the prevalence rate was between 5% and 8%. Among the developed countries, New Zealand had the highest use rate at 4%. The Kingdom of Tonga, with a total population of 100,000 (World Bank, 1993) was the only country with a reported use rate of 46% (Parsons, 1990).

But it may be contended that these figures are misleading. It may be argued that even though the percentage of married women in the reproductive age group using injectables is low, the percentage of contraceptors using injectables could be high. Even viewed that way, the use rate does not seem appreciably high. Indonesia, Thailand, Honduras, Jamaica, and Mexico were the only five countries where the percentage of contraceptors using injectables was between 10 and 20% (Liskin *et al.*, 1987). For the majority of the rest of the countries, the use rate among contraceptors was between < 0.5% and 5%. Between 1987 and 1991, use of Depo-Provera in Thailand increased from 9% to 12% and in Indonesia,

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1. The advertising firm, Mudra Diversified was responsible for the publicity during the launching of Depo-Provera in India in 1994.

between 1987 and 1994, its use increased from 10% to 15% in married women of reproductive age (Lande, 1995).

In 1994, of the 57% currently married women using contraception in Indonesia, 21% were using injectable contraceptives (Sugihartatmo, 1998). South Africa appears to be the only country which reported a very high prevalence of use of 23% and this group formed approximately 41% of the total contraceptive users. A break-up of this figure reveals that the 'share' of injectables is only 3% in the 79% of the white population using modern methods, whereas it forms 27% (or more than half) of the 49% users among the Black population in South Africa. Currently about 12 million women are said to be using the injectable contraceptives (Lande, 1995).

The figures that are provided are mostly the use rates for both the injectable contraceptives (Depo-Provera and Noristerat) combined together. Even if one accepts that Depo-Provera is the "largest used" preparation, the overall prevalence of use is very low and except for South Africa, Depo-Provera does not appear to be an important contraceptive of choice even in countries with no restrictions on its use.

In the developed countries where Depo-Provera is registered, it is primarily prescribed to mentally disabled women (Kinch, 1982; Egan et al., 1993), women with a drug addiction problem (Mark, 1983), indigenous population such as the native Americans in the USA (Anon, 1987) and Maori women in New Zealand (Paul et al., 1997), sexually active adolescents (Isart et al., 1992; Pinkston-Koenigs & Miller, 1995; Cromer et al., 1998), coloured women (Hollander, 1996; O'Dell et al., 1998) and women from low income groups (Westhoff et al., 1995; Davidson et al., 1997).

2. Effectiveness

"In five DEPO-PROVERA clinical studies using DEPO-PROVERA, the 12 month failure rate for the group of women treated with DEPO-PROVERA was zero (no pregnancies reported) to 0.7 by Life-Table method... The effectiveness of DEPO-PROVERA is dependent on the the patient returning every 3 months for reinjection".

(Upjohn Co., 1993)

"The effectiveness of the injectables depends on the timing of the first injection, adherence to the injection schedule, and the injection technique".

(Lande, 1995)

The theoretical-effectiveness of any contraceptive method is the maximum effectiveness of that method i.e., its effectiveness when used without error, when used perfectly, when used exactly according to instructions. On the other hand, use-effectiveness takes into consideration all users of a method i.e., those who use the method without error and those who are careless (Hatcher *et al.*, 1976).

In the injectable depot preparations, the use-effectiveness and theoretical-effectiveness are considered to be closely matched. In fact, one of the stated reasons for the development of injectable depot preparations has been to obviate the need for sustained motivation and to eliminate the problem of lack of compliance (Soonawalla, undated). Injectables are said to "minimize or entirely remove the obstacle of patient (*sic*) compliance from contraceptive efficacy" (Gold, 1995).

Depo-Provera is considered to be highly effective with a 'typical'[2] pregnancy rate of 0.3 per 100 women in the first year of continuous use (Upjohn Co., 1993). However, in order to maintain this 'typical' rate, it is recommended that the first injection be given in the first five days of a normal menstrual cycle. Depo-Provera administered beyond this narrow window period may not be effective in preventing pregnancy.

In a prospective study from Brazil, 30 women aged 18 to 40 years were administered Depo-Provera between days 8 and 13 of their menstrual cycle (5 women on each day) (Petta *et al.*, 1998a). Ovarian function was determined by serum levels of E2 and progesterone, and follicular development by vaginal ultra sound. In 9 (30%) of the women, Depo-Provera did not prevent ovulation. All ovulations occurred in women receiving the injection between days 10 and 13 of the cycle and all the ovulations occurred within 3 days of the injection. In these women cervical mucus was also studied for sperm penetration (Petta *et al.*, 1998b). Only in 90% of the women, the cervical mucus became hostile to sperm penetration within 24 hours. Since, currently there are no reliable markers to identify the contraceptive effect of Depo-Provera on the cervical mucus, the authors have recommended that the women should be provided with a back up method of contraception for 7 days when the first injection of Depo-Provera is provided after the seventh day of the menstrual cycle.

In 7930 Thai women, the pregnancy rate among those who received Depo-Provera in the first eight days of the menstrual cycle was 1.6 per 100 women compared to 6.2 for those who received the injection after the ninth day (Liskin & Quillin, 1983).

The discontinuation due to method failure (pregnancy) in the Family Planning Programme of Indonesia, where the injectable has been available since 1974, has been reported to be 3% giving a failure rate of 1.6% (Sugihartatmo, 1998).

Thus, when the injectable contraceptive is actually put in a field situation, where consistent and correct use may not be possible, the

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2. Typical— includes those not following directions exactly.

failure rate could go upto 6 or more per 100 women i.e., twice as high as the 'typical' failure rate of an intra-uterine contraceptive device. (Upjohn Co., 1993)

That this is a high possibility can be seen from the recommendation of the International Medical Advisory Panel of the International Planned Parenthood Federation. According to their recommendation, "ideally, a woman should start progestogen-only injectable contraceptives during the first seven days of a menstrual cycle .... However, the request for injectable contraceptive at another time during the cycle should not be made a condition for rejecting her at that time if the possibility of a pregnancy can be ruled out" (IMAP, 1992).

The currently available routine pregnancy tests are not sensitive enough to detect a pregnancy before a period is missed. The immunologic urine assay is accurate only within 25-28 days after conception i.e., after 2 weeks of a missed period. Thus, it is not possible to rule out pregnancy before a period is missed.

In Philippines, where Depo-Provera has been re-introduced in the period following the USFDA ruling, in a follow-up of a group of 'new' contraceptors, it was found that 40% of the interviewed women (n = 899) had not received their first injection during the right time of their reproductive cycle (Arenas, 1995).

Failure to return within the specified period for the next injection is not confined to women from developing countries. For 23% of acceptors attending a hospital in New York (n = 159), the single reason for discontinuation was "appointment non-compliance" (Polaneczky & Liblanc, 1998). Of the 65% of women from a centre in North Carolina who discontinued in one year (n = 510), almost 20% were considered discontinuers because they waited longer than 16 weeks to return for an injection (Potter et al., 1997).

In the calculation of use-effectiveness or 'typical' failure rates, the continuation rate of a contraceptive also has an important bearing.If discontinuation is taken as an indication of unacceptability, almost half of the original acceptors find the method unsatisfactory.

A randomised, multinational, comparative clinical trial with the two injectable contraceptives, Depo-Provera and Noristerat, showed that for Depo-Provera, the gross cumulative discontinuation at 1 year due to both medical and non-medical reasons, was 28.8 (± 1.6) per 100 women years (WHO, 1977). Among non-medical reasons for discontinuation, almost 50% was due to failure to return within the specified period of time for the next injection. The study had a stringent requirement that the injection be given at a regular interval of 12 weeks within a narrow margin of 15 days. In Chandigarh, one of the participating Indian centres, 82% of women in the Depo-Provera group dropped out of the study by the end of one year.

In another multinational study carried out by the WHO, the discontinuation rate was even higher; the gross discontinuation rate at 1 year for Depo-Provera was 51.4 (± 1.3) per 100 women years (WHO, 1983).

This high rate of discontinuation was seen in a later study comparing 100 mg and 150 mg of Depo-Provera also. In this study, the cumulative discontinuation rate at 12 months for all reasons was 40.7 (for the 100 mg) and 41.2 (for the 150 mg) per 100 woman years (WHO Task Force, 1986a).

The pattern of high discontinuation among Depo-Provera acceptors is seen in the reports that have appeared after the period of USFDA approval also. The 12 month discontinuation rate was 58% (Davidson *et al.*, 1997), 71% (Hollander, 1996), both from populations in the USA and 41.1% in a population from Bangladesh (Rahman *et al.*, 1996).

Thus, in a field situation, the overall failure rate or 'typical' failure rate will be far higher than the stated 0.7 because of failure to receive the first injection within the extremely narrow window period, failure to return for the repeat injection within the appropriate time period and due to the high drop out rate in the first twelve months of use.

Safety Aspects of Depo-Provera

I. Impact on the Health of the Women

3. Menstrual Disturbances

"Warnings

Bleeding irregularities:

Most women using Depo-Provera Contraceptive Injection experience disruption of menstrual bleeding patterns. Altered menstrual bleeding patterns include irregular or unpredictable bleeding or spotting, or rarely, heavy or continuous bleeding."

(Upjohn Co., 1993)

3.1. Bleeding Disorders

Depo-Provera is known to cause menstrual disturbances which are unpredictable.

The Phase III clinical trials carried out by ICMR with Depo-Provera found that in a total of 131 women given 150 mg Depo-Provera every three months, for whom data was collected over a period of eight months, there was a high incidence (50%) of heavy and/or prolonged bleeding or amenorrhoea (ICMR, 1975).

The Institute for Research in Reproduction (IRR), Bombay, reports its findings in two groups of women: one group received Depo-Provera within the first 10 days of delivery, the other receiving the injection at least 6 months after delivery (IRR, 1975). In Group II (interval), the 'acceptable' bleeding increased from 33% to 54% but the 'aberrant' bleeding (bleeding for 9-20 days in a segment) increased from 6% to 18% by the end of 6 months. In the postpartum group, there was an increase in amenorrhoea as the months of use increased.

In the multinational comparative clinical trial of the WHO, 70.6% of the women on Depo-Provera did not experience even one normal

cycle[3] for the duration of the study (WHO, 1978). Such women tended to have more than the normally expected 5 days of blood loss during each episode especially during the first three injection intervals. There was an excess of spotting days and episodes lasting more than 10 days were also more frequent. There was pronounced variability and unpredictability of bleeding events with Depo-Provera.

In report after report dealing with bleeding disorders, the data is presented as discontinuation due to the event. Therefore in most of the studies reporting bleeding disorders, it becomes difficult to assess the incidence in a group of women exposed to Depo-Provera.

If discontinuation is taken as an indication of the incidence of morbidity, a large multinational study by WHO has shown that at the end of 12 months, the cumulative discontinuation rate due to bleeding problems with Depo-Provera was 15.0 ($\pm$ 1.0) (WHO, 1983). In another multicentric study comparing Depo-Provera 100 mg and 150 mg, 12% of the women discontinued because of spotting, irregular, prolonged or heavy bleeding (WHO,1986).

Menstrual diary records of a total of 5257 women using nine different methods of contraception showed that women using Depo-Provera had totally unpredictable patterns, with infrequent but prolonged bleeding/spotting episodes[4] (Belsey & Task Force, 1988a). For the first six months, women using Depo-Provera had longer bleeding/spotting episodes than women using any other form of contraception. In the first reference period[5], 25% of subjects using Depo-Provera had episodes whose average length exceeded 13 days. By the last reference period, although their mean episode lengths were similar to the other seven groups, some women continued to experience consistently long episodes. One woman

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3. In this study, a normal cycle was defined as a cycle of 26-35 days duration and 2 to 8 days of bleeding.
4. In the analysis of the menstrual diaries, a bleeding/spotting episode was defined as any set of one or more bleeding or spotting days bounded at each end by two or more consecutive bleeding-free days.
5. A 90-day reference period was used, with the first reference period commencing on the date of treatment.

using Depo-Provera 100 mg had episodes with an average length of 26 days in her fourth injection period. Depo-Provera produced the greatest variability in bleeding pattern not only between women but even within women.

In general, only about 10% of Depo-Provera users are found to have normal cycles in the first year of use. Table-1 gives the menstrual pattern among users of Depo-Provera from the several WHO multicentric studies carried out between 1983 and 1988.

Further analysis of the menstrual diaries to examine the associations between bleeding patterns and demographic variables showed that among women using Depo-Provera, there was a marked regional variation in bleeding patterns (Belsey *et al.*, 1988a). For instance, in the first reference period, women from South East Asia had longer episodes (8.0 days), shorter intervals (26.0 days), and thus more bleeding/spotting days (21.0 days) than women in any other region.

Obese women had fewer number of bleeding/spotting days and episodes than thinner women, and also tended to have shorter episodes and longer intervals (Belsey *et al.*, 1988b). Women whose last pregnancy had ended in abortion had more bleeding or bleeding/spotting days, in all four reference periods, than women who had had a live birth.

In the study of menstrual diaries of the 5257 women referred earlier, the analysis presented in the report is on a subset of the original cohort (Belsey & Task Force, 1988b). The women included in the analysis were those who continued in their clinical trial for one year, and were capable of and sufficiently motivated to completing a diary for a full year. 45% of the women from the sample were excluded from analysis in the the Depo-Provera 150 (mg) group because they did not fulfill one of the above mentioned criteria. Further more, the purpose of the analysis was not to describe the 'true' experience (or incidence) but to compare bleeding patterns due to different methods.

Discontinuation rates due to bleeding problems are reported to be an underestimation of true morbidity. In the report presenting the

Table 1. Menstrual Patterns Among Users of Injectable Contraceptives, WHO Multicenter Studies, 1983-1988

Percentage Experiencing Bleeding Patterns

Type of Injectable	Months	Number of Diaries	Regular Patterns	Amenorrhea	Infrequent Bleeding	Irregular Bleeding	Frequent Bleeding	Prolonged Bleeding	Total Variations from Regular Pattern
DMPA	0-3	509	9.0	10.6	15.7	46.0	17.7	43.4	91.0
	4-6	406	6.9	23.9	25.8	35.7	10.5	27.7	93.1
	7-9	311	6.4	37.0	24.8	27.7	8.3	17.3	93.6
	10-12	241	8.3	38.6	27.8	17.9	6.6	16.5	91.7

Note : Patterns are defined for 90-day observation periods:
Regular Patterns —Three episodes of bleeding or spotting each lasting about five days.
Amenorrhea— No bleeding
Infrequent bleeding—Fewer than two bleeding or spotting episodes.
Frequent bleeding—More than four bleeding or spotting episodes.
Irregular bleeding—A pattern in which the difference between the longest and shortest bleeding-free intervals is more than 17 days.
Prolonged bleeding—At least one bleeding or spotting episode lasting 10 days or more.
A bleeding episode is defined as requiring the use of a pad or other protection. A spotting episode does not require protection.
No comparable data for NET EN are available.
[a] Some subjects appear in more than one category.
Source: Lande, 1995:11.

analysis of menstrual diaries, Depo-Provera users who reported non-menstrual side effects as the reason for discontinuation and in those who were lost to follow up, a considerable proportion had discontinued the method because they were unwilling or unable to tolerate their bleeding patterns (Belsey & Task Force, 1988b). This was despite the fact that Depo-Provera users tolerated far greater menstrual disruption than women using any other method.

The WHO has also noted that there is some evidence to show that a few women may experience episodes of heavy endometrial bleeding if Depo-Provera is started too soon after childbirth and that it is advisable to wait for 6 weeks following delivery before administering the contraceptive (WHO, 1990).

Thus, depending on the timing of the administration of the inject- able contraceptive, i.e., whether it is given in the immediate post partum period or later, or whether it is after an abortion or a live birth, the bleeding pattern would vary. Populations also show wide regional variations in the pattern of bleeding disturbances.

The attitude towards bleeding disorders due to Depo-Provera has been to minimize its importance as a health effect and to be more concerned about the possibility of discontinuation of the contracep- tive by the user (see box). Concern has also been expressed that the psychological, social and cultural effects of disruption of bleeding patterns may make the method unacceptable (WHO, 1990).

> "I think the most important consideration with all of these drugs is the woman's perception of biological effects and not the biological effects per se. In other words, if women continue to use drugs despite the fact that they disrupt menstrual cycle, then these drugs are better contra- ceptives in the public health sense than other forms of contraception which women use for shorter period of time but which disrupt menstruation to a lesser extent. I feel that we should not be too concerned with minor menstrual disturbances but focus on those major disturbances which either affect the continuation rates or the health of the subjects" (Gray, 1980).

Mechanism of bleeding disorders

Internationally, concern has been voiced about the possible mechanisms for the bleeding disorders with Depo-Provera. A symposium convened by the WHO on 'Endometrial bleeding and Steroidal contraception' concluded that the data base on this was meagre, confusing and sometimes controversial and that no simple solution was in sight (Diczfalusy, 1980).

In this symposium, the different hypotheses put forward to explain the mechanism of bleeding due to steroidal contraceptives included the possibility of changes in the endothelial lining of the blood vessels in the endometrium manifested mainly as underdevelopment of arterioles and degenerative changes in the venules (Maqueo, 1980). In a small number of cases, the lesions of the vascular endothelium was also noticed in several other organs. Disruption of the normal mechanism of coagulation (Paton et al., 1980) and the possibility of increased lysosomal permeability leading to a "slow leak" of lysosomal contents (Wilson, 1980) are some of the other hypotheses put forward to explain the mechanism of pathological bleeding with Depo-Provera.

Adverse effects of bleeding disorders

Although a vast amount of literature exists on bleeding disorders with Depo-Provera, till recently no study has systematically examined the adverse effects of bleeding on the health of the woman. In fact, bleeding disorders are dismissed as 'minor' side effects. Bleeding problems can affect haemoglobin levels. Without changing haemoglobin levels appreciably, heavy and prolonged bleeding can cause a fall in serum ferritin levels indicating a depletion of the iron stores in the body. For instance, women with the levonorgesteral subdermal implant who reported excessive bleeding and expressed a desire to have the device removed, showed a fall in serum ferritin levels even though their haematocrit levels were higher than the control group (Faundes et al., 1987).

Alterations in the menstrual cycle can have other important implications as well. Koblinsky and colleagues have pointed out that

menstrual cycle patterns may be a fundamental determinant of women's health status and that alterations in menstrual function may influence many disease processes including the natural resistance to meastatic spread (Koblinsky *et al.*, 1993). For instance, timing of surgery during the menstrual cycle has been observed to influence survival period of women with breast cancer. Women undergoing surgery during the luteal phase of the cycle had a 84% ten-year survival compared with 54% ten-year survival rate in those operated during the follicular period.

Treatment for bleeding disorders

Till date, no appropriate and adequate treatment has been evolved for the treatment of bleeding problems with Depo-Provera. In mid seventies, therapy with long acting estrogen, quinesterol, one of the first attempts tried out by the ICMR to control bleeding disorders, proved ineffective (ICMR, 1975).

With their concerns focused largely towards discontinuation rates due to bleeding disorders, proponents of Depo-Provera recommend that appropriate counselling and the bedside manner (physician's attitude) would be sufficient to prevent women from discontinuing the contraceptive (Fraser, 1982).

> *"Counselling is very important for the woman before she starts the method, and on each occasion when she comes back for repeat injections. If she has such a menstrual disturbance, she should be repeatedly assured that this is not a health hazard or a long term health problem for her. It is a nuisance value only. If she is unable to tolerate the disturbance, it will unfortunately usually lead to discontinuation of the method"* (Fraser, 1982).
>
> However, in the next breath as it were,
>
> *"It is clear that the bleeding disturbances associated with DMPA and NET-EN are poorly understood and that urgent research is necessary to clarify pathophysiological mechanisms and improve management"* (Fraser, 1983).

The WHO observed that if the woman reports prolonged bleeding, she should be evaluated for anaemia and should receive appropriate iron therapy if indicated (WHO, 1982). However, as stated earlier, a woman with bleeding problems may have normal haemoglobin and haematocrit values but have a low serum ferritin levels. In such cases, estimation of haemoglobin level may not be an adequate evaluation.

In 1982, the WHO recommended the following regimen "recognizing however, that its effectiveness has not been adequately demonstrated",

"If the bleeding is heavy and prolonged:

(a)   The woman should first be evaluated for possible causes of the bleeding (other than the steroid) and also treated for anaemia. Ferrous sulfate should be given if indicated.

(b)   A woman experiencing moderate and prolonged— or heavy —bleeding due to the steroid should be given $25 \mu g$ of estradiol, one tablet 3 times daily for 3 days.

(c)   If this therapy is ineffective, or if the woman initially presents with very heavy bleeding, she should be given 5 mg of estradiol cypionate in an oily suspension intramuscularly; and this dose should be repeated once if the bleeding does not stop within 24 hours. Additional medical advice may be indicated at this stage.

(d)   If, after having received 10 mg of estradiol cypionate intramuscularly, the bleeding continues, the woman should be referred for possible dilatation and curettage." (WHO, 1982).

Eighteen years have passed since the report of WHO was published. The treatment recommended by the WHO remains essentially unchanged. Ethinylestradiol for 14-21 days or a single 21 day course of monophasic combined OC is recommended. In addition to the above, the WHO in 1990 recommended that in case of heavy and prolonged bleeding, a second dose of Depo-Provera may be given early but not earlier than 4 weeks after the previous dose (WHO, 1990).

In Phillipines, one of the developing countries to re-introduce Depo-Provera after the USFDA ruling, the following treatment is advocated:

"With regard to the management of the side effects and complications, spotting and light bleeding should be managed by reassurance.

Moderate bleeding is considered normal and is expected in 25-30% of women in the first 3-6 months of use. 14-21 low-dose or medium dose OCs may also be given if reassurance does not help.

Heavy bleeding is unusual; therefore OCs should be given for 14-21 days. In the event of especially heavy bleeding other possible causes should be evaluated; the estrogen level should be doubled for 3-7 days, followed by one OC for 11-14 days; and an injectable estrogen (5 mg estradiol cyprionate IM) should be given. Bleeding will stop for more than 50% of women by 12 months and amenorrhoea will occur in 75-80% of users during continuous DMPA use". (Huber, 1994)

Ibuprofen and other non-steroidal anti inflammatory drugs (other than aspirin) are also being recommended as they are perceived to help by blocking the synthesis of prostaglandins which induce bleeding (Lande, 1995). Oral Depo-Provera is another recommendation (Archer et al., 1997).

A multicentre placebo-controlled randomized clinical trial by the WHO (1996) has, however, called into question the use of estrogens to effectively deal with the bleeding problems. In this study, 44% of the women (456 of 1035 women) reported bleeding episodes lasting for more than 7 days during the first six months of use. Of these 278 (61%) requested treatment and were randomly assigned to one of the three groups: one group receiving 50 μg ethinyl estradiol (n=90); the second group receiving 2.5 mg estrone sulfate (n=91); and the third group a placebo (n=97), all receiving the treatment daily for 14 days. In 93% of women from the ethinyl estradiol group

the bleeding episode stopped as compared to the 76% in the estrone group and 74% in the placebo group. The ethinyl estradiol advantage was, however, marginal with the shortening of the bleeding days by 1 and spotting days by 3. Three months after the treatment, there were no differences between the three groups in their vaginal bleeding pattern. None of the other 'therapies' have been evaluated for their efficacy.

The manufacturer too does not seem to have any effective remedy for the bleeding disorders. All that the Upjohn Co. (1993) advices is that in case abnormal bleeding persists or is severe, "appropriate" investigations should be instituted to rule out the possibility of organic pathology and "appropriate" treatment should be instituted. The drug literature however does not state either what these appropriate investigations are, or what the appropriate line of treatment should be.

The indiscriminate use of estrogens to control the bleeding in Depo-Provera users takes away its supposed advantage of not having any estrogenic effects.

> *"There will be menstrual problems with the injectables. Lesser bleeding with Depo is not a side effect. I will call it a mechanism of action. Endometrium cannot be puffy. Strong progesterone does not allow for puffiness. This is called an anticipated effect. In fact, Depo-Provera is the method of choice in women with menorrhagia"*
> (Dasgupta, former Drugs Controller of India, 1994).

Das Gupta, the former Drugs controller of India, recommends that Depo-Provera should be the contraceptive of choice in women who have heavy periods or menorrhagia (see box) (Anandani & Sathyamala, 1995a). This is with the hope that the woman will develop amenorrhoea as a consequence of taking Depo-Provera, thus providing symptomatic relief from menorrhagia. This recommendation is unsupported by any published study. The Upjohn's literature recommends that Depo-Provera be administered to only those women with normal menstrual cycle.

3.2. Amenorrhoea

*"As women continue using Depo-Provera, fewer experi-
ence intermenstrual bleeding and more experience amenorrhoea.
By month 12 amenorrhoea was reported by 55% of women, and by
month 24 amenorrhoea was reported by 68% of women using
Depo-Provera".*

(Upjohn, 1993)

Amenorrhoea is the other major menstrual problem with long-term
use of Depo-Provera. In a multinational comparative clinical trial
with a menstrual experience of 372.5 woman years with Depo-
Provera, prolonged amenorrhoea increased with the duration of use.
By the end of 1 year, 35% of the women developed 'total'
amenorrhoea (WHO Task Force, 1978). The percentage of women
with amenorrhoca of more than 90 days increased from 33.9 in the
first 6 months, 54.1 in the 6-12 months interval, and finally to 61.9
in the 18-24 months interval. (WHO, 1983).

Pathophysiology of amenorrhoea

Amenorrhoea is a reflection of the state of endometrium in the users
of Depo-Provera. In the absence of priming with estrogen, continu-
ous administration of a progestin in sufficient dose is known to
abolish the menstrual cycle for as long as it is given and leads to
ovarian and endometrial atrophy (Goodman and Gilman, 1985).

A WHO technical report admits that the administration of
injectable progestogen results most frequently in endometrial
atrophy (WHO, 1971). Compared to combined oral contraceptives,
endometrial atrophy usually occurs earlier during treatment with
injectable progestational agents (Dallenbach-Hellweg, 1980).

The atrophic effect of Depo-Provera has also been seen in other
studies. 100 recently post partum women were given Depo-Provera
three monthly for 1 year (Mishell, 1968). A total of 275 endometrial
biopsies were obtained from 86 women who returned at least once.

The percentage of atrophic[6] biopsies showed a gradual increase so that one year after the first injection nearly 40% of the biopsies (from 37 women) revealed atrophic endometrium. There was a positive correlation between the amount and frequency of bleeding and endometrial histology.

57 women were administered 6 monthly Depo-Provera as a contra-ceptive (Khoo, 1971). Of the 282 biopsies obtained at 2 monthly intervals, it was more difficult to obtain biopsies from the 4th to the 6th months of treatment. In these last months of treatment, 32%, 43% and 29% of the biopsies were unsuccessful after the first, second and third injection compared with 18%, 25% and 25% in the corresponding early period. The disassociation between epithelial and stromal response was most notable 4 months after each injec-tion; while the epithelial glands underwent progressive atrophy, the stroma reacted with oedema and decidual transformation. There was both direct effect of Depo-Provera on the endometrium and an indirect effect by changing the estrogenic and progestational milieu in the woman. At each interval, there was a high non-response. For instance, at the 3rd injection, the total number of biopsies done at two monthly intervals were 16, 18 and 13 of the 57 women recruited into the study.

Of the 138 women recruited into a clinical trial on Depo-Provera, 65 endometrial biopsies were obtained at the first follow up (Mukherjea et al, 1980)[7]. Of this, 72.5% were of a proliferative nature, 12.3% belonged to a quiescent group and 15.4% revealed atrophic endometrium. After 2 years of study, only 24 biopsies were examined of which 8.33% were quiescent in nature, and 87.5% showed a characteristic atrophic endometrium.

From these studies it appears that endometrial atrophy is noticed even after one dose of Depo-Provera and the probability increases with successive doses.

6.   When no endometrium was found in spite of several attempts to obtain tissue with the biopsy curette, the endometrium was interpreted to be atrophic.

7.   This is one of the studies submitted by Upjohn to the Drugs Controller of India as an 'Indian' study.

Adverse effect of amenorrhoea

Amenorrhoea with Depo-Provera has been stated to be associated with a reduction in the incidence of anaemia, an apparent benefit of "ligfiter" bleeding, (Mudra Diversified, 1994). Two of the published studies from India have not unequivocally demonstrated this presumed effect.

In a cross sectional study from India, 20 women using Depo-Provera, (16 of whom were amenorrhoeic at the time of haemoglobin estimation) and 30 on Noristerat were compared with women on IUD (n=275), combination pill (n=106) and a control group of 428 women seeking contraceptive advice (Prema, 1979). Mean levels and frequency distribution of haemoglobin in women who had used Cu IUD upto 3 years, Lippes's Loop upto 10 years, combined pills upto 18 months and injectable progestogens upto 12 months were essentially similar to that seen in the control group. That the use of hormonal contraceptives, either injectables or oral pills, was not associated with any improvement in haemoglobin status was considered "surprising". The explanation put forward to explain this unexpected finding was that the extent of decrease in menstrual blood was too small to make any impact and that some of the metabolic alterations like changes in folic acid metabolism may have had an adverse effect which could have neutralised the possible beneficial effect of decreased menstural blood loss.

In a group of undernourished, lactating women from low income group in Bombay and Hyderabad, haemoglobin and heamatocrit, serum iron levels prior to and following the use of Depo-Provera (for 12 months), were measured (WHO Task Force, 1986). There were no alterations in the levels of haemoglobin and haematocrit following use of Depo-Provera for one year. In Hyderabad, where the sample population was significantly different from the control group of non-lactating women in nutritional status, the serum iron level showed a significant increase after Depo-Provera (from 57.6 μg/ml initially to 79.0 μg/ml at 9 to 12 months, $p < 0.01$). However, the sample population (n=34) in whom this measurement was done was just a small proportion of the number (n = 170)

recruited initially since there was a high discontinuation rate because of prolonged amenorrhoea and irregular and unpredictable bleeding. In the group from Bombay there was a slight fall (from 93.7 to 82.0 μg/ml) which was not statistically significant. The report does not describe the menstrual pattern in these women following the administration of Depo-Provera.

In a recently published multinational study, the haemoglobin and ferritin levels of women using oral contraceptives, Depo-Provera, Norplant, Copper IUD and Chinese stainless steel ring IUD, were compared with women initiating contraception (Task force for Epidemiological Research on Reproductive Health, UNDP *et al.*, 1998). Between 1988 and 1992, in the cross sectional component of the study, 221 women using Depo-Provera were recruited in the study from Chiang Mai (n=95), Dhaka (n=51), Karachi (n=25), and Khon Kaen (n=50) and compared with 791 women initiating contraception (controls). The mean duration of use of Depo-Provera was 45.9 months in Chiang Mai, 21.3 months in Dhaka, 14.0 months in Karachi and 13.5 months in Khon Kaen. The Depo-Provera users differed significantly from the control population in 'time since last menstrual period' (Chiang Mai); age, parity, frequency of intake of meat/week, time since last pregnancy ended, duration of previous menses, time since last menstrual period, and standard of living (Dhaka); time since last pregnancy and last menstrual period (Karachi); and parity, time since last pregnancy, duration of previous menses and time since last menstrual period (Khon Kaen).

In all the 4 centres, the mean haemoglobin levels were higher in the Depo-Provera users, but it was significant only in Chiang Mai (difference in mean 0.7gm/dL, $p \leq 0.001$) and Khon Kaen (difference in mean 0.9gm/dL, $p \leq 0.001$). The mean serum ferritin levels were higher in three centers but was significant only in Chiang Mai (difference in mean 6.6 μg/L $0.001 < p \leq 0.01$). The mean ferritin level in Dhaka in Depo-Provera users was higher than the controls (44 μg and 57 μg respectively) but was not significant.

When the results were pooled together, Depo-Provera users had

higher haemoglobin levels (difference 0.6 gm/dL, SE 1.5, p≤0.001) and ferritin levels (difference 18 μg/L, SE 6.3, 0.001, p≤0.01).

In the longitudinal component of the study, the initiators of Depo-Provera, who formed part of the control population of the cross sectional component, were followed up for 12 months. Since the sample sizes were not adequate, the report presents only the results from Dhaka for haemoglobin which was significantly higher as compared with levels at the time of initiating the study.

The results did not support one of the hypotheses tested—that the increase in haemoglobin and ferritin levels would be most marked in women with the lowest standard of living.

There are several methodological flaws in this study. Of the 221 Depo-Provera users recruited for whom admission characteristics are presented, haemoglobin levels are presented for only 147 women (66.5%); in the case of ferritin levels, analysis of 131 women are presented (59.3% of sample). The 'dropout' in the number from the control population is 21.5% in the analysis of ferritin levels. While the analysis presents 'adjusted' mean values, it is not clear

"In countries where anemia is common among women, an effect—either positive or negative—of a widely used method of contraception on this problem would have substantial implications for public health. In spite of the potential importance that contraceptive use may have with respect to iron deficiency, very little information was available at the start of this study on the effect of contraceptive methods on iron status, particularly in populations with a high prevalence of anemia. Furthermore, many of the available studies had suffered from shortcomings such as lack of appropriate comparison groups or had been too small to allow meaningful conclusions to be reached..... There were very few data on the effects of depot medroxyprogesterone acetate (DMPA) and Norplant[(R)] *implant use on iron status and anemia"* (Task Force for Epidemiological Research on Reproductive Health, UNDP et al., 1998).

what they were adjusted for. The results would need to be adjusted for several variables as the population characteristics differed widely between the four centers. This would hold for the analysis of results pooled from all the centres as well. The report does not describe the menstrual patterns of the women in the sample.

Depo-Provera users from Chiang Mai had a mean duration of use of 45.9 months. This group was probably amenorrhoeic, manifesting total amenorrhoea. An increase in haemoglobin and ferritin levels in this group is therefore not surprising. The Depo users from Karachi and Khon Kaen had a mean duration of use of less than 14.0 months and in Dhaka, the women had used Depo for a mean duration of 21.3 months. In the group from Dhaka, the increase in haemoglobin was the least from among the four groups (0.48 gm/dL) and the serum ferritin level was lower than the control group. The women in Karachi, Khon Kaen and Dhaka were probably a group consisting of women manifesting either bleeding or amenorrhoea. This is perhaps why the serum ferritin levels have not shown any appreciable change in these groups. The absolute levels of serum ferritin in Depo users and control population in all these three centers as well as the control group in Chiang Mai is lower than normal levels. Finally, it needs to be remembered that this is a cross sectional study and the Depo users recruited in this study are the survivors of a cohort initiating Depo-Provera contraceptive.

This when seen in the light of the high dropout rate of 40-60% by the end of one year in almost all the studies reported in the literature, would indicate that the women recruited in the study are a very small, highly selected population of the original cohort of initiators. This could perhaps be the reason why even after trying for several years and from several countries, only 221 women using Depo-Provera could be included in the study. The results of this study appears to show that in those women who have tolerated the initial menstrual disturbances and have accepted amenorrhoea with Depo use, there is a likelihood of increase in haemoglobin and serum ferritin levels. But before we accept this to be conclusive the questions raised earlier need to be resolved. In this study, all the Depo-users appear to have had their last menstrual period 3.5 to 6.0

days prior to recruitment. This seems highly suspect as long-term Depo-Provera use leads to amenorrhoea.

Adverse effects of endometrial atrophy

In castrated monkeys administered high doses of progestogens an apparently irreversible atroph with hyalinization of the stroma has been noticed (Dallenbach-Hellweg, 1980). No reported study has examined the reversibility of endometrial atrophy in women receiving Depo-Provera.

No effective treatment for such complications has also been reported. But for women who "may not accept prolonged amenorrhoea, and may ask for a 'period' to be induced", a single 21-day course of a combined oral contraceptive containing 50 μg of an estrogen has been recommended "if estrogens are not contraindicated" (WHO, 1990). Switching over to a monthly injectable, cyclofem (25 mg Depo-Provera + 5 mg estradiol cypionate) is yet another recommendation for inducing cyclical bleeding (Piya-Anant et al., 1998). Currently trials are underway and WHO is studying the effect of switching Depo-Provera users who "dislike" amenorrhoea to cyclofem (Lande, 1995).

Endometrial atrophy due to Depo-Provera and the consequent secondary amenorrhoea could have a bearing on the woman's future fertility status. This is a serious complication in women desiring more children after the discontinuation of the contraceptive[8].

> "Women may need extra help to get through the first months of frequent or irregular bleeding.... Also important is reassurance that amenorrhea is not harmful: Lack of menstrual bleeding does not mean that women are pregnant or that blood is building up in their bodies.... Providers can reassure clients that bleeding returns to normal after stopping progestin-only injectables" (Lande, 1995).

8. See section nine for discussion on endometrial atrophy and return of fertility.

4. Hypo-estrogenic state

Administration of progestogenic agents in high doses inhibits pituitary secretion of Lutenizing Hormone (LH) and Follicle-Stimulating Hormone (FSH). With Depo-Provera, since cyclical secretion of pituitary LH and FSH is suppressed, the circulating levels of the main ovarian hormones oestradiol and progesterone are also significantly suppressed (Fraser & Weisberg, 1981). Prolonged administration of progestogens results in decreased endogenous production of estrogen leading to a relatively estrogen deficient state although studies have shown conflicting results.

Following an injection of Depo-Provera, serum estradiol levels are initially in the early to mid-follicular phase range (approximate mean 50 pg/ml) (Mishell, 1996). Serum estradiol levels begin to rise about four months after a single injection when the medroxy progesterone levels in the blood fall below 0.5 ng/ml. For women who have used Depo-provera for several years, serum estradiol levels range between 10 and 92 pg/ml with mean levels of about 40 pg/ml.

75 Thai women who had been long term Depo-Provera users (> 3 years) had their estradiol levels compared with non-Depo users (Virutamasen *et al.*, 1994). Venous blood for estimating serum estradiol was taken at the 12th week of administration of Depo-Provera in users and within 5 days after menstrual bleeding cessation in controls. The individual serum levels of medroxy progesterone acetate at the 12th week of injection was 4.1 ± 1.1 nmol/L. The mean serum level of estradiol in the long term Depo-Provera users (>7 yrs) ranged from 122.9 pmol/L to 167.7 pmol/L which was not significantly different from that of the controls (141.9 to 195 pmol/L).

In another small study (Taneepanichskul & Patrachai, 1998), serum estradiol levels were measured in 50 Thai women who had used Depo-Provera for a variable period of time (mean duration of use 59.1 ± 30.7 months). The mean serum estradiol level was 52.7 ± 15.1 pg/ml. An earlier report of the study compared the serum estradiol of these women with 41 current users of Norplant, a levonorgestrel sub-dermal implant (Taneepanichskul *et al.*, 1997a). The serum estradiol levels of Depo-Provera users which "ranged into normal" for the follicular phase was significantly lower than that of the women with Norplant. When the serum estradiol of Depo-Provera users was compared with that of IUD users (n=50), serum estradiol levels were significantly reduced in Depo-Provera users (52.67 ± 25.1 pg/ml compared with the controls 147.51 ± 91.9 pg/ml) (Taneepanichskul *et al.*, 1997b).

In 153 out of a sample population of 185 women aged 17 to 52 years (mean age 33.3 years) who had used Depo-Provera for between 1 and 16 years with amenorrhoea of more than 1 year, attending a family planning clinic in Manchester, the serum estradiol level was < 150 pmol/L (Gbolade *et al.*, 1998). Serum estradiol levels have been significantly lower in Depo-Provera users (55.7 pg/ml) as compared with a group of women not using hormonal contraceptives (149.9 pg/ml) (p < 0.001) (Paiva *et al.*, 1998).

The hypo estrogenic state induced by Depo-Provera could lead to any one of the following effects.

4.1. Climacteric-like syndrome

Menopause is defined as the time at which menstruation ceases, whereas climacteric is the phase of waning ovarian activity and is a period of adjustment between active and inactive ovarian function. The period of climacteric may occupy several years before and after menopause.

The "menopausal syndrome" refers to a group of physical symptoms commonly experienced in the climacteric period due to estrogen deficiency (Shaw *et al.*, 1992). But as they often predate

the menopause, they are also a result of relative estrogen deficiency as well as to fluctuating levels of ovarian hormones. The symptoms are varied, insidious and can frequently be misdiagnosed as endogenous depression, migraine and general debility. However, a confident diagnosis of menopausal syndrome can be made in the presence of vasomotor symptoms and vaginal dryness in association with depression, tiredness and headaches of recent onset.

The characteristic symptoms of estrogen deficiency state are hot flushes, night sweats, headaches, loss of energy and depression. The estrogen deficiency state can also lead to osteoporotic changes. The etiology of hot flushes is unclear but when associated with insomnia, lethargy, and giddiness, may lead to falling attacks with the possibility of femoral neck fracture in osteoporotic women. There are other widespread atrophic changes and women often report thin, dry skin, brittle nails, and loss of hair. These occur due to generalised loss of collagen tissue which could also result in frequent muscle and joint pain.

In the Physicians' Desk Reference of 1994, under Depo-Provera preparation of 100 mg and 400 mg used in the treatment of endometrial and renal carcinoma, it is mentioned that although the age of the patient constitutes no absolute limiting factor, administration of the drug may mask the onset of the climacteric (PDR, 1994). For the same reason, the WHO also cautions the use of Depo-Provera contraceptive in women over the age of 40 years (WHO, 1982; 1990).

Peters (1986), Professor and Chairperson, *Institut De Pharmacologie*, University of Lausanne, has expressed concerns about the possibility of early climacteric with the long term use of progestogens. According to him, total amenorrhoea may be mixed up with an early climacterium and lead to a feeling of loss of womanhood; and that high progestogen contraception is often accompanied by a loss of libido and pain during intercourse, the latter being partly due to an absence of pre-coital moisture. There are accompanying skin changes, dry scaly to sometimes thickened texture of skin.

The Drug literature of Upjohn Co. (1993) lists out a long list of adverse drug reactions with Depo-Provera. When the symptoms are clubbed together in a syndromic complex, a different picture emerges. Under "Adverse Reactions", it refers to a clinical study on "over" 3,900 women who were administered Depo-Provera for more than 7 years[9]. According to their report of the study, more than 5% of women reported headache, nervousness, dizziness, asthenia (weakness or fatigue); and 1 to 5 % reported decreased libido or anorgasmia, backache, leg cramps, depression, insomnia, no hair growth or alopecia, hot flushes and arthralgia.

The study referred to is a collaborative study conducted between February 1965 and October 1971, on 3857 women (Schwallie & Assenzo, 1973). The median study duration was 12 months (90th percentile, 45 months). By the end of one year of study, the cumulative drop out rate was 40.6/100 women and by 2 years, it was 58.5/100 women. 17.1% of the women reported headache, 10.8% reported nervousness, 5.4 % reported dizziness and 5.4% decreased libido. These figures are probably an underestimation of true morbidity because as the authors note "there is a possibility that some of the women listing desire for pregnancy or for personal reasons for dropping out of the study may actually have dropped due to drug-related reasons which they did not wish to disclose to the interviewer or clinician".

A more recent study (Solheim, 1992) assessed the impact of Depo-Provera on the quality of life of women who had used the contraceptive for at least one year. Of the 451 Swedish women who answered a mailed questionnaire,

- a decrease in libido was reported by 25% users which was associated with both duration of use as well as the woman's age (the younger the woman, the greater the loss of libido);

- vaginal dryness was reported by 13% of the users and was significant when correlated with loss of libido ($p<0.001$);

- night sweats by 35%;

- and hot flushes by 12%.

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9. No reference is given in the drug information sheet.

A retrospective review of clinical data of 363 women administered a total of 2,298 injections of Depo-Provera since 1973 (20 years) in one gynaecological practice in Melbourne, Australia, showed that the most commonly reported side effect was "superficial" dyspareunia or reduced libido which was reported by 8% of the women (Fraser, 1994).

A 30 month prospective study using "convenience" sample of subjects documented physical and symptomatic changes in adolescent girls using Depo-Provera (Matson, 1997). Fifty three, mostly African-American women (mean age 16.5 ± 1.3 years), attending the Department of Pediatrics in a medical college in the USA were given Depo-Provera. In order to decrease menstrual irregularity, the first two doses were given at an interval of 6 to 8 weeks (recommended interval is 12 weeks), the subsequent injections were given at 12 weekly intervals. A questionnaire administered at each visit elicited reported symptoms of headache (25%), fatigue (23%), and decreased sexual desire (15%). (The other reported symptoms were weight gain - 27%, irregular periods - 24%, and abdominal pain-18%). 60% of the users had discontinued by one year.

Atrophic and post partum like changes in cervical smears and biopsies have been observed in long-term Depo-Provera users (Valente et al., 1998).

Women with symptoms of hypoestrogenic side effects have been advised to undergo a serum estradiol level test and if necessary take appropriate replacement therapy (Nelson, 1996). The UK Clinical and Scientific Committee has recommended that serum estradiol levels should be estimated in Depo-Provera users with more than two years of amenorrhoea and/or the presence of climacteric-like symptoms. A serum estradiol level under 150 pmol/L on two separate occasions has been suggested as indicative of a need for estrogen supplementation or a change of contraceptive method (Cayley, 1998).

Loss of libido has been reported in males administered Depo-

Provera and this is one of the reason why Depo-Provera is not recommended in males as a contraceptive[10].

In males, Depo-Provera is used to 'control' sexual deviance. Although not included in the labelling, in U.S.A., Depo-Provera has been prescribed parenterally for the management of paraphilia (homosexual, heterosexual, or bisexual pedophilia; heterosexual voyeurism; sexual sadism or exhibitionism; and transvestism) in males. The drug has been shown to decrease erotic imagery and the intensity of erotic cravings in most of these males (AHFS,1994).

In 1983, the state of Oregon in the USA passed a Bill directing the Mental health Division to establish a pilot programme to administer Depo-Provera to "persons convicted of any sexual offence involving forcible compulsion" (Oregon legislative assembly, 1983).

At least till 1984, Depo-Provera was being used routinely at the Johns Hopkins Bisexual psychohormonal clinic when a Public Citizen Litigation Group from Washington DC, filed a petition to the USFDA to regulate this unapproved use (Glitzenstein et al., 1984).

*"**Sentenced. Roger Gauntlett,** 41, an heir to the Upjohn pharmaceutical fortune, who had pleaded no contest to a charge of sexually assaulting his stepdaughter, 14; to a year in jail and five years of 'chemical castration' with Depo-Provera, which decreases the male sex drive and is manufactured by Upjohn; in Kalamazoo, Mich. With the drug, said Circuit Court Judge Robert Borsos, 'it is now possible to castrate a man and at a future time reverse the effects'. Both sides plan to appeal."*

(Time,1984)

10. Depo-Provera is known to have a contraceptive effect in males also.

4.2. Depo-Provera and osteoporotic changes

Demineralisation of bones is another consequence of the hypo-estrogenic effect of Depo-Provera[11].

The adverse effect of Depo-Provera on the integrity of bone was one of the concerns expressed by members of the panel of the Public Board of Inquiry set up by the USFDA in 1983. Following this, a study was carried out in New Zealand on a group of Depo-Provera users to assess changes in bone density during use (Cundy *et al.*, 1991).

In a matched case-control study, 30 current users of Depo-Provera with a minimum of five years' previous use were compared with 30 premenopausal control and 30 postmenopausal controls matched for several determinants of bone density. The lumbar spine and femoral neck density were assessed by dual energy densitometry.

The study found that compared with premenopausal controls, Depo-Provera users had significantly reduced bone density in the lumbar spine (mean difference 7.5%; 95% CI, 1.9%, 13.1%; p = 0.002); and in the femoral neck (mean difference 6.6%; 95% CI, 0.8%,12.3%; p = 0.007). When the bone density in Depo users was compared to postmenopausal women, the Depo users had greater bone density in the lumbar spine (8.9%; 95% CI, 4.3%, 13.5%; p = 0.001) but in the femoral neck, the difference was less (4.0%; 95% CI, -0.4%, 8.5%; p = 0.04). Depo-Provera users were thus found to have bone density values intermediate between those of normal premenopausal and postmenopausal controls.

Although the controls had not been matched for cigarette smoking, one of the risk factors for osteoporosis and a potential confounder, the effect of smoking was controlled in the analysis by eliminating the discordant pairs. The mean difference in bone density between Depo-Provera users and premenopausal controls remained similar.

According to the authors of this study, the degree to which bone

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11. Partial glucocorticoid activity of the progestogen has been postulated as another mechanism for the osteoporotic activity of Depo-Provera (Breckwoldt, 1994)

density was reduced in Depo-Provera users was comparable with that seen in other estrogen deficiency states and outweighed the possible suppressive effect that progestogens may have on bone turnover.

Cundy and colleagues concluded that the reduction in bone density due to Depo-Provera use is not of a sufficient magnitude to place otherwise healthy premenopausal women at an immediate risk of developing fracture. However, reductions in bone density of this order have been estimated to increase lifetime fracture by 30 to 100%. It is of concern that in this study rapid loss of bone occurred within a short term of use of 3 years. The study is not in a position to comment on the reversibility of such loss on discontinuation of Depo-Provera.

A physically active, 33 year-old woman demonstrated a 12.4% drop in femoral neck bone mineral density (BMD), 6.4% drop in lumbar BMD and 0.8% drop in total BMD with the subsequent development of a tibial stress fracture while on depot medroxyprogesterone acetate. Bone mineralization rapidly improved and the stress fracture resolved on discontinuing the contraceptive (Harkins, 1999).

*   *   *

A 39 year old, thin, caucasian woman on depot medroxyprogesterone acetate for 17 years developed multiple fractures after falling off from a stationary horse. Densitometry revealed significant osteopenia (Mark, 1994).

Following the study by Cundy and colleagues in New Zealand, there have been several studies on the osteoporotic effect of Depo-Provera.

Changes in bone density of 75 long-term Depo-Provera users (duration of use more than 3 years) from Thailand were compared with 75 women, matched for age, non-Depo users (Virutamasen *et al.*, 1994). There were no significant changes in the trabecular bone

in the group with a history of duration of use of more than 7 years
(n = 25).

A randomized clinical trial on women seeking contraceptive advice
in a Family Planning unit of University Hospital in Uppsala,Sweden,
allocated 22 women to either Depo-Provera contraceptive or the
subdermal implant (Naessen *et al.*, 1995). Only 19 completed the 6
months follow up (9 in Depo-Provera group and 10 in the implant
group) and 4 women refused to accept any form of radiation for
bone density assessment. At 6 months, there was a decrease of
0.41% BMD in forearm density of the Depo-Provera group which
was not significantly different. Depo-Provera increased bone turn-
over (serum calcium 2.33 to 2.38, P = 0.38; urine hydroxy proline
creatinine ratio - 12.1 to 24) and bone formation (serum osteocalcin
1.2 to 1.61) but the differences were not significant.

Bone density in 185 women, aged 17-52 years, attending Family
Planning clinics in Portsmouth and Manchester, with a history of
Depo-Provera use between 1 and 16 years was compared with
population mean for women aged 20-59 years (Gholade *et al.*,
1998). In women reporting amenorrhoea for more than one year or
any woman using Depo-Provera for more than 5 years, the mean
bone density of the lumbar spine compared to population means
was not signigicantly different (z score -0.332; 95% CI. - 0.510 to
0.154). There was no significant difference in the mean density of
the femoral neck.

Mean bone density levels in a group of 183 Depo-Provera users
enrolled in a Washington State Health Maintenance Programme,
showed lower levels at all anatomic sites examined (spine, femoral
neck, and trochanter) as compared with 274 non-Depo users en-
rolled with the same programme (Scholes *et al.*, 1999). The associa-
tion remained after multivariate analysis (p < 0.01). The major
differences in bone density between users and non-users was
highest in the age group of 18-21 years with the bone density of
femoral neck 10.5% lower (p < 0.01) and the differences were
consistent across all anatomic sites (p < 0.01).

Another cross sectional study on 50 Brazilian women who had used

Depo-Provera for one or more years found a reduction in the distal portion of the forearm which was not significantly different from the control group of 50 women who had never used hormonal methods (Bahamondes *et al.*,1999).

One study that examined the bone density in post menopausal women who were former Depo-Provera users (n = 34) found that in women with a history of duration of use of more than 2 years, there was a tendency towards lower bone densities in the lumbar spine (1.6%), femoral neck (3.1%) and total body (0.5%) as compared with 312 post menopausal women with no history of previous use of Depo-Provera (Orr-Walker *et al.*, 1998). These differences were, however, not significant.

Only one reported study has examined the reversibility of bone loss on discontinuation of Depo-Provera (Cundy *et al.*, 1994). 14 women who had used Depo-Provera for at least 3 years (range of use 3 to 17 years) were studied while taking the contraceptive and after having stopped it and 22 long-term users (range of use 5 to 20 years) were studied while they were on the contraceptive. These two groups were compared with 18 women who had never used Depo-Provera. In the first group of women discontinuing Depo, 12 women resumed menstruation between 2 and 24 months (median 8 months) and 2 remained amenorrhoeic till the end of the study. Bone density in the second to fourth lumbar spine was measured twice in each woman at an interval of 9-20 (median 12) months. Bone density in the lumbar spine was on average 9.0% lower in the first two groups compared with the controls (p < 0.02). Bone density at the femoral neck was 5.7% lower but was not significantly different from the control group. At the second measurement, in the group that had discontinued Depo-Provera, at one year, bone density in the lumbar spine increased by 3.4% (95% CI, 1.6% to 5.2%) compared to its values at first measurement but the values continued to be lower than the control group by 11.2%. In the small sub-group of women (n = 8) from this group an increase in bone density in the lumbar spine was observed between 12 and 24 months (p < 0.002). Bone density in the femoral group did not change in any of the three group at first follow up. Though the authors conclude that the bone loss

with Depo-Provera may be almost completely reversible even after long-term use, the study design (cross sectional), recruitment of the subjects (no details given, with probable selection bias) and loss to follow-up of 6 women in the first group does not lend weight to this conclusion.

Despite the variability in the results of all these studies and their limitations, a general consensus seems to be emerging that Depo-Provera does have a negative effect on bone mass.

To minimize the risk of osteoporosis with Depo-Provera, a daily dose of 1200 mg of elemental calcuim and daily exercise of long bones have been recommended (Sharts-Hopko, 1993).

Implications for Indian women

Demineralisation of bone with Depo-Provera has serious implications for women in India who are under weight (a predisposing factor for osteoporosis) and manifest a high prevalence of calcium deficiency.

A study carried out in India, found that osteoporosis was common among women over the age of 34 years (Nordin, 1966). The study assessed the prevalence of osteoporosis by examining hand and spine films chosen at random from the files of the x-ray department from hospitals in Bombay, Delhi, Patna and Vellore. It was found that a reduction in spinal density and metacarpal cortical thickness was apparent at an earlier age among Indians as compared to their western counter parts. Moreover, contrary to western countries, fracture of hip was found to occur *at all ages* (emphasis theirs), which seemed more to reflect the age distribution of osteomalacia rather than osteoporosis. While this report has several limitations, the findings serve as an indication of the high prevalence of osteoporosis and osteomalacia in India.

The chief investigator of the New Zealand study, Cundy, has recommended that women with more than one risk factor for osteoporosis (family history, underweight, cigarette smoking, European or Asian origin) should have bone mineral density measurements undertaken if they are considering Depo-Provera use on a

continuing basis. Women in the lower third of the normal range should be advised to consider other contraceptives (Stehlin, 1993).

It is unlikely that in India bone mineral density measurements will be taken prior to administering Depo-Provera[12]. Moreover, it may not be advisable to subject large numbers of women to such invasive procedures and add to the long-term risks of Depo-Provera.

Implications for the health of lactating women

Studies on Depo-Provera have so far concentrated on the effect of breast milk on the growth and development of infants. Little attention has been paid on the effect of Depo-Provera on the health of the lactating woman. It is our contention that administration of Depo-Provera during lactation could have a serious adverse effect on the health of the breast feeding woman because of its association with demineralisation of bone.

Almost all of the additional calcium required during pregnancy is for the growth of the fetus. The fetal pregnancy requirement is about 30 gm of which the term fetus has 27.5 gm, the placenta 1 gm and the maternal fluids and tissues about 1 gm. During lactation, the requirement of calcium is 1.2 gm per day, the human milk having a calcium content of 25-35 mg/100 ml. The extra needs of calcium and lactation are best met by increasing the milk intake. The skeleton of an adult has 1000 gm to 1200 gm of calcium and it would appear that when the dietary source of calcium is restricted or there is failure of absorption, calcium will be mobilised from the maternal skeleton, especially during lactation (Menon et al., 1986).

It is now known that demineralisation occurs irrespective of additional calcium intake. A recent study has shown that even if the dietary source of calcium is increased in lactating women, demineralisation of bone takes place with prolonged breast feeding (Sowers et al., 1993). This prospective cohort study carried out in Michigan, U.S.A., showed that bone mass density in the breast

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12. Primary health centres in India lack facilities to carry out even simple tests such as haemoglobin estimation, pregnancy testing, or x-ray chest in patients with suspected tuberculosis etc.

feeding woman decreases even when her nutritional status is good and she takes supplementary calcium during lactation.

98 women grouped according to lactation duration were followed for 12 months and BMD was measured by dual energy x-ray densitometry of the proximal femur and lumbar spine. Women with lactation duration of more than six months or longer had a mean BMD losses of 5.1% and 4.8% at the lumbar spine and femoral neck respectively when compared with baseline levels. These levels were significantly different ($p < 0.0001$) from both the control groups : women who bottle-fed their infants or breast fed for less than 4 weeks and women in the intermediate lactation group (women with lactation duration of 2 to 5 months). Women who breast-fed for 0-1 month did not show loss of BMD at either bone site.

At the 12 month examination, among those who weaned between 6 and 9 months, the average spine and femoral BMD values had returned to baseline values. In contrast, women continuing lactation had an average femoral BMD value that was 3.5% less than baseline which just missed being significant ($p=0.06$). The average spine BMD value was 2% less than baseline ($p = 0.03$). Although in women who breast-fed for shorter durations, the BMD at lumbar spine returned to normal between 6 months and 1 year of parturition, it was not clear if there would be complete recovery at the femoral neck site.

The loss of BMD in lactating women in this study was despite an adequate intake of more than 1250 mg/day dietary calcium to meet the infant's nutritional need. The calcium intake in the lactating women was significantly greater than that in either of the two controls. The bone loss was associated with excess bone resorption rather than depressed bone formation. The ingestion of even high levels of calcium was inadequate to suppress active resorption in the relatively low-estrogen environment of lactation.

In this context, the studies carried out on bone density, specifically that by Cundy and colleagues (1991) on osteoporosis and Depo-Provera assumes a new significance. If Depo-Provera is administered to lactating women, the low-estrogen state of lactation that

would have existed till the resumption of ovulation in the normal state would now be prolonged due to the ovulation suppression effect of Depo-Provera.

Moreover, in India with a wide prevalence of osteomalcia, and where rural women on an average breast feed for more than 2 years, administration of Depo-Provera would prolong the period of demineralisation of bone. Increasing dietary calcium intake is also not a possibility that exists for the majority of Indian women who are poor.

It is important to prevent pregnancies during lactation and space pregnancies to give the woman adequate time to recover and reduce her calcium loss. However, this should not be at the risk of aggravating and prolonging the period of bone loss by the administration of Depo-Provera.

Lactation should thus be an absolute contraindication for the administration of Depo-Provera in Indian women, the greater proportion of whom are under and malnourished (Sathyamala *et al.*, 1994).

Implications for the health of the adolescents

The WHO recommends, with certain reservations, that adolescence as such should not be seen as an absolute contraindication for the use of Depo-Provera (WHO,1990). The study by Cundy and others (1991) on the association of bone loss and use of Depo-Provera, however, raises concern about its use in adolescents.

In children, 50% of the skeletal mass destined for maturity has been achieved by the age of 11 years. A further 45% is achieved by 18 years and the remainder after this age. During the peak height velocity periods, calcium may be retained as bone in amounts upto 400 mg per day in girls. In boys, maximum bone growth occurs at the same time as peak height velocity whereas in girls the bone growth is not so dramatic and tends to be maximal a little after peak height velocity (Parkes *et al.*, 1977).

In the developing skeleton, bone mass continues to increase until the closure of epiphysis. In late adolescence (between 14 and 17 years of age in girls), although there is not much additional spurt in
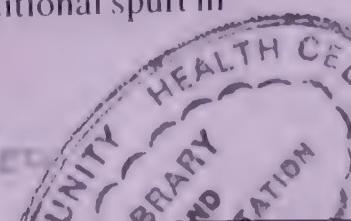
linear skeletal growth, remaining epiphysis such as those of femur, humerus, symphysis pubis and sterno-clavicular junction become fused, sometimes as late as the early 20s (Nelson's Text book of Pediatrics, 1992).

The peak adult bone mass achieved and the subsequent rate of bone loss are the major factors that determine a woman's susceptibility to postmenopausal osteoporosis.

Depo-Provera, a contraceptive that causes loss of bone in users should not be administered during adolescence since this is the period of maximum bone growth and for the closure of epiphysis. An adverse effect on bone development in this period due to Depo-Provera use could lead to greater morbidity during future pregnancies and an increased susceptibility to postmenopausal osteoporosis.

Bone density measurement of four lumbar vertebrae of a group of postmenarcheal, adolescent girls aged 12 to 21 years from a general adolescent clinic at Ohio State University Medical College, accepting one of three methods, Depo-Provera, (n=15); Norplant, (n=7); and oral contraceptives, (n=9) were compared with that of a group (n=17) using either a barrier method or reporting abstinence from sexual intercourse (Cromer et al., 1996). After one year of exposure, mean bone density in Depo-Provera users decreased by 1.5% whereas it increased by 2.9% in the controls ($p < 0.02$). Among those who continued to receive Depo-Provera for 2 years, (n=8), the mean bone density decreased to a total of 3.12% ($\pm$ 0.85 SE) and increased in the control group by 9.49% ($\pm$ 1.35 SE). Differences in the characteristics of the two population (ethinicity, exercise, age etc.) were not sufficient to explain these findings. The authors suggest that the low levels of estrogen associated with Depo-Provera may not be adequate for girls of the postmenarcheal age to produce optimal bone mineralization.

In the developed countries, poor compliance with other safer contraceptive methods like the condom is one of the major reason for targeting adolescents for Depo-Provera use. Unwanted teenage pregnancies (mostly out of marriage), in the USA for instance, is one million each year and is considered a problem of public health significance in that country (Davis, 1996). In a prospective study of

53 low-income adolescent girls (mean age 16.5 years) from a pediatric primary care in the USA, 17% had been prescribed Depo-Provera because of a history of poor pill compliance and 6% because of mental retardation (Matson *et al.*, 1997).

Compared to their counterparts in Sweden and Netherlands, the American pediatricians one more likely to prescribe Depo-Provera to teenaged girls (Cromer *et al.*, 1998).

The enthusiasm of American pediatricians for prescribing Depo-Provera to adolescents was apparent even before the USFDA granted approval for Depo-Provera contraceptive in 1992. Questionnaires mailed to physician members of the Society of Adolescent Medicine and the North American society of Pediatric Adolescent Gynecology showed that of the 616 (60%) who responded, 87% had prescribed contraceptives to adolescents and 41% had prescribed Depo-Provera for an average of eight years (Koenig *et al.*, 1995). Adolescent Depo-Provera users fell into three major groups: mentally retarded adolescents (43%), those with medical conditions that precluded estrogen (24%) and others (teen mothers, those with history of poor compliance with other methods etc). 27% of physicians acknowledged providing Depo-Provera to minors without parental consent.

In the recently held meeting of the Institute for Research in Reproduction in Bombay, the participants recommended that although not contraindicated, it was advisable not to use Depo-Provera in adolescents (Tejuja & Juneja, 1998). Elsewhere, clinicians have been advised to recommend calcium supplements for adolescents of Depo-Provera users because "adolescents in general are not inclined to be big milk drinkers" (Anon, 1998). A drug safety newsletter has advised that caution should be exercised in prescribing long-term Depo-Provera especially in young adolescents (girls aged less than 16 years) who may not have yet reached peak bone mass (Cromer, 1999).

Depo-Provera and Fluorosis

India is one of the 19 nations having serious health problems due to excess fluoride in drinking water. It is estimated that about 25 to 30 million persons in 150 districts in India are suffering from varying

grades of fluorosis (Sawhney, 1994). Surveys carried out by the Rajiv Gandhi National drinking water mission have revealed that of the 15 states identified as endemic for fluorosis, Uttar Pradesh, Gujarat, Andhra Pradesh and Tamil Nadu are the worst hit with 50 to 100% of the districts affected. In Punjab, Haryana, Madhya Pradesh Maharahtra and Karnataka 30 to 50% of districts are affected and in Delhi, Jammu & Kashmir, and Kerala, less than 30% of the villages are afected. The highest recorded fluoride level in the drinking water was in villages from Haryana which reached a maximum of 38.5 ppm.

Fluorosis affects the permanent teeth in young children and in adults skeletal fluorosis affects bones, tendons. ligaments followed by pain and stiffness of the back, joints of both limbs and limitations of neck movements. The affected persons manifest gastrointestinal symptoms such as loss of appetite, nausea and abdominal pain as well. In Samaypur village of Faridabad district, for instance, 56.6% of inhabitants were found to be afflicted with skeletal flourosis, 65.9% with dental fluorosis and 52.4% reported gastrointestinal problems.

In a population based study carried out between 1963 and 1993 covering 400,300 children residing in non-endemic area ($F^- \leq 1.0$ ppm) and endemic ($F^- > 1.0$ ppm) villages in India examined the interaction between fluorosis and the calcium intake in the diet (Teotia & Teotia, 1994). The percentage of children with inadequate calcium intake was comparable in both the population. Their baseline calcium intake were identical at less than 0.5 gm per day. Decayed teeth per hundred children were maximum in 5 to 10 year olds who had inadequate calcium intake and were exposed to high fluoride intakes.

A randomized clinical trial over five years with elemental calcium supplements in this population showed that adequate dietary calcium intakes provided an effective control and prevention of dental fluorosis indicating an interaction between fluoride and calcium.

In women living in endemic fluorosis villages in India, and whose diets are inadequate in calcium, it may therefore not be advisable to administer Depo-Provera with its demineralization effect on bones.

5. Depo-Provera and cardiovascular disease

"Warnings

Thromboembolic Disorders

The physician should be alert to the earliest manifestations of thrombotic disorders (thrombophlebitis, pulmonary embolism, cerebro-vascular disorders, and retinal thrombosis). Should any of these occur or be suspected, the drug should not be readministered"

(Upjohn Co., 1993).

According to the WHO, cardiovascular effects associated with the use of estrogen containing oral contraceptives have not been found with injectable progestogen-only contraceptives and that there appears to be no significant changes in blood coagulation or in the incidence of thromboembolic disease (WHO, 1990).

The publicity material produced by Mudra Diversified is more crisp and to the point: "Thromboembolic and ocular disorders[13] are associated with hormonal products containing estrogen, for example oral contraceptives. Since Depo does not contain estrogen, this is not a concern" (Mudra Diversified, 1994).

This is what we believed in the seventies. The high estrogen component of the combined oral contraceptives was indicted as the cause of the now well documented thromboembolic disorders associated with its use. This led to the development of preparations with lower and lower doses of estrogen. However, it was observed that some of the vascular effects seen with estrogen preparations persisted despite the low estrogen content of the new products (Spellacy, 1982). Progestogens are now known to have their own independent cardiovascular effects.

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13. These effects should not be classified under "ocular" disorders.

Elevation of blood pressure, alteration in serum lipids especially on the high density lipoproteins could lead to an acceleration of cardiovascular changes. Hormone preparations that simultaneously elevate low-density-lipoprotein cholesterol (LDL-C) and decrease high-density-lipoprotein cholesterol (HDL-C) cause the most concern with regard to coronary heart disease.

Effect on Blood Pressure

In a retrospective study, blood pressure records of women receiving 150 mg of Depo-Provera three monthly were reviewed (Leiman, 1972). The duration of the study period was two years but only 70 women had received more than 6 injections. Out of the total 1507 women who had received at least one dose of Depo-Provera, 1050 women had their blood pressure recorded every three months. Significant changes, i.e., >20mm Hg systolic or >10 mm Hg diastolic *either up or down* occurred in 252 women (24%). Of these, despite the fluctuation, in 165 (15.7%) the blood pressure remained within the normal range. 87 women (8.3%) had significant changes in blood pressure which took them out of the normal range. The diastolic level changed more frequently than the systolic and in both, the change was twice as likely to be in the upward direction. Women who were hypertensive (160/100 and above) at the initial recording were 2-3 times more likely to have a downward fluctuation. Of the 24 patients exhibiting the most severe rise in blood pressure, in 22 the rise was sudden occurring over a period of 3 months at most. In 15 the rise occurred with the administration of the first injection. The changes in blood pressure did not correlate with changes in weight.

No significant changes either in diastolic or systolic blood pressure were noticed in a randomized Phase III multicentric clinical trial with Depo-Provera 100 mg or 150 mg three monthly (WHO, 1986). Three women with hypertension were admitted in violation of protocol. However, they became normotensive, two by the first follow up visit and the third by the third visit. Three women were asked to discontinue because of hypertension during the course of

the study, the rise in blood pressure occurring within the first six months, and the woman on Depo-150 mg registering a blood pressure of 160/115. A further 15 women had one measurement above the defined limit of normality (diastolic > 90 mm Hg and/or systolic > 140 mm Hg) during the course of the study and 4 women on more than one occasion. They were not advised to discontinue the use of Depo-Provera. The combined mean change in systolic blood pressure was -0.1 mm Hg per year (95% CI, -1 to 1 mm Hg) and for diastolic was +0.3 mm Hg (95% CI, -0.3 to 0.9 mm Hg). The study had a high drop out rate with 40.7% of the 100 mg schedule and 41.2% of the 150 mg schedule discontinuing by the end of one year.

Depo-Provera appears to have a dual effect on blood pressure. Considering the fact that Depo-Provera seems to change blood pressure level either up or down, differences in mean values may not be the appropriate measurement to assess change. The results for the two groups (one with elevation in BP and the other with a fall in BP) should be treated as two separate groups manifesting two different effects of the contraceptive. A further limitation of the study is that the results of both the dosage regimens have been clubbed together to give combined mean values.

Direct effect of Depo-Provera on both the adrenals and pituitary can be one of the mechanisms that could explain its dual effect on blood pressure. A group of 22 menopausal women with inoperable or disseminated breast cancer who were administered oral MPA (300 mg tid for at least 6 weeks) before any serum samples was taken, were compared with 28 postmenopausal women with advanced cancer before hormonal or cytostatic treatment was started (Veelen et al., 1984). Women given MPA showed a marked fall in cortisol and androgen levels whereas the Adrenocorticotropic hormone (ACTH) levels varied widely. It was postulated that if MPA had a direct inhibitory effect on adrenal steroidogenesis, low cortisol, low androgens and elevated ACTH levels would have been expected. On the other hand if MPA had an inhibitory effect on ACTH release, low ACTH levels should have been found. The wide variation in

ACTH levels found in this study was postulated to be caused by a direct effect on ACTH release by medroxy progesterone acetate itself or a metabolite. The formation of a cortisol-like 21 hydroxy-lated metabolite was also described.

Effect on Blood Lipids

Most studies have found that Depo-Provera has an adverse effect on serum lipids and is associated with an elevation of LDL cholesterol and lowering of HDL cholesterol (Lande, 1995).

Serum HDL-C level in 23 women receiving Depo-Provera for at least 1 year were compared with a control group of 23 IUD users (Kremer *et al.*, 1980). Serum HDL-C concentration was signifi-cantly lower in the Depo-Provera group than in the IUD group ($t=4.3$, $p<0.001$). The serum HDL-C level was not influenced by the lapse of time after a Depo-Provera dose. This was an unexpected result because the average serum concentration of the drug is not uniform throughout the interval.

Serum lipids in 157 women who had received Depo-Provera continuously from 6 to 84 months were compared with 166 matched controls who were not on hormonal steroids or pregnant at least six months before the blood tests (Liew, 1985). The study group showed an alteration of lipid levels. Triglycerides were initially decreased being significant at 36 months ($p<0.01$) and returned to normal at 60 months. Cholesterol levels increased with duration of use and were significantly higher at 24, 36 months ($p<0.05$) and 60 months ($p<0.001$). A prospective one-year study in women admin-istered Depo-Provera three monthly has also shown a 15% decrease in HDL-lipids (Enk *et al.*, 1992).

A multicentric comparative clinical trial carried out by the WHO (1993) on women who had used Depo-Provera, with women using IUD as a control group has concluded that long term use of Depo-Provera induces moderate changes in lipid metabolism which are unfavourable in terms of risk for atherosclerosis.

Serum lipids of 50 women aged between 25 and 40 years, from three centres (Bangkok, Christchurch and Mexico city) who had been

using Depo-Provera continuously for a minimum of 4 to maximum of 6 years were compared with a control population of 120 women using IUD. Serum lipids measured at the time of admission to the study showed significant differences, after controlling for alcohol drinking, smoking and quetelet index, between the Depo-Provera users and the controls as well as among the three centres. Compared with the controls, in Bangkok, the Depo group had a mean LDL-C level significantly higher by 24%; in Christchurch 13% lower HDL-C, 18% lower apo AI, 39% higher apo B mean levels and 39% lower apoAI/B ratio; and in Mexico city, the only significant difference was a 14 % higher LDL-C in DMPA users. Changes in serum lipid measurements during the 13-week injection interval showed a 6% decrease in HDL-C at 2 weeks, a 12% decrease in apo AI at 4 weeks and an 11% drop in the apo AI/B ratio at 8 weeks post-injection.

The authors concluded that these changes were attributable to Depo-Provera use and these could be termed moderate changes in lipid metabolism which are unfavourable in terms of risk of atherogenesis. Their recommendation is that before a woman initiates Depo-Provera use, her existing underlying risk for atherogenesis should be assessed by clinical history and her lipid profile obtained in high risk cases.

Reviewers have echoed the WHO's concern that the moderate changes in lipid profile could increase the risk of atherogenesis (Kauntiz, 1994). The observed increases in low-density lipoprotein cholesterol and the increase in high-density lipoprotein cholesterol have not been followed up to determine if they increase the long-term risk of cardiovascular disease (Westhoff, 1996).

Effect on Blood Coagulation

Injectable progestogens are also known to increase the risk of coagulation of blood in experimental animals by significantly lowering prothrombin time, increasing Factor X activity, increasing collagen induced platelet agggregation and ADP induced platelet aggregation (Sivakumar et al., 1992-93).

Thromboembolic phenomena has been reported with Depo-Provera

use. In a study coordinated by the Upjohn Co., 11 women out of the total 3857 recruited, developed thrombophlebitis and thromboembolism during the study (Schwallie & Assenzo, 1973). One of these women had a fatal pulmonary embolus associated with disseminated carcinoma of the lung. Four women developed deep vein thrombophlebitis of the lower extremities and one had a right subclavian vein thrombosis. The report does not provide any details with regard to the characteristics of the women thus affected, the timing of the event with the Depo-Provera injection, or the eventual fate of these women.

It has been argued that the studies on hormonal contraceptive and lipid metabolism carried out on the western population may not be relevant to undernourished Indian women. Because of the lower triglyceride and cholesterol levels in the undernourished population, it has been suggested that Indian women may be at a lower rate of cardiovascular disease risk than their western counterparts. Data has shown that though Indian women with cardiovascular disease had higher lipid levels than normal Indian women, the levels were far below their western counterparts (ICMR, 1981). Thus, it may be the magnitude of change and not the actual values that determine the cardiovascular risk in a population.

Despite all these findings, a review by Fredriksen (1996) recommends Depo-Provera for women over 35 who smoke because it is not associated with any increased thromboembolic disease and tries to persuade the reader that the package labeling of the drug is "based on trials of high doses of DMPA as a cancer treatment" and therefore not relevent to its use as a contraceptive.

6. Depo-Provera and Carbohydrate metabolism

"Warnings

Carbohydrate Metabolism

A decrease in glucose tolerance has been observed in some patients on Depo-Provera treatment. The mechanism of this decrease is obscure. For this reason, diabetic patients should be carefully observed while receiving such therapy".

(Upjohn Co., 1993)

Depo-Provera administered to 157 women for a mean duration of 43.4 months with a matched control group of 166 women showed significant changes in carbohydrate metabolism (Liew *et al.*, 1985). Glucose tolerance was significantly decreased while insulin response was significantly lowered at 30 minutes and increased at 150 minutes. Glucose intolerance increased with duration of use and was significantly higher than the controls at 48 and 60 months.

A study on a group of undernourished lactating women from two Indian centres (Bombay, Hyderabad) and one centre from Thailand (Chiang Mai) showed a difference in fasting glucose level between initial reading and at 12 months in both Hyderabad and Chiang Mai ($p < 0.05$) (WHO Task Force, 1986b). In Chiang Mai, glucose tolerance at 120 minutes showed a marginal difference which was nevertheless significant at $p < 0.01$ level.

Clinical trials with oral contraceptives containing either 50 or 30 μg of ethinyl oestradiol and 150 μg of levonorgestrel on a group of undernourished women from India (Bombay and Hyderabad) and Thailand (Chiang Mai) showed a significant reduction in

glucose tolerance in all the centres (ICMR, 1985). At the end of one year, 24.4% of the sample population from Bombay developed impaired glucose tolerance curves and 2.4% had diabetic curves. The corresponding figures for Hyderabad was 9.7 and 2.8. No significant difference existed between the two formulations suggesting that the reduction of estrogen component did not reduce the effect on glucose tolerance. It has been suggested that the risk of aberrant glucose tolerance is as great in malnourished women as in the well-nourished women.

Alteration in Weight

With Depo-Provera use, both an increase and a decrease in weight has been observed. Mishell and colleagues (1968), have reported that in their study equal numbers of women gained or lost weight while on Depo-Provera. Of the 42 women whose weights were recorded before treatment and after one year of Depo use, 10 gained more than 10 lbs and 5 lost more than 10 lbs.

A retrospective study of 816 women using Depo-Provera through a Family planning clinic showed an alteration in weight for 92% of the study population (Leiman, 1972). 66% showed a gain in weight and 26% lost weight. The mean gain was 4.4 lbs (SD ±8.5) over a six month period of time. Initial obesity did not predispose to excessive weight gain and there were no significant differences in age, parity between the group that experienced the largest weight gain and the rest of the study population. 20% of the women gained >10 lbs over a six month period and excessive gains upto 69 lbs were recorded.

A study coordinated by the Upjohn Co., which covered 991 women for a median study duration of 24 months using Depo-Provera 300 mg six monthly showed an average gain in weight of 8 lbs at 24 months (Schwallie & Assenzo, 1972). With Depo-Provera 150 mg three monthly Schwallie and Assenzo (1973) have also reported that mean weight increased from 135.9 lbs at the initial reading to 144 lbs at 24 months, to 152 lbs at 60 months. A mean increase in body weight of 1.9 Kgs at 12 months and 3.3 Kgs at 24 months was

observed in the multicentric WHO trial also (WHO, 1983).

In all these studies, differences in mean has been used to assess effect of Depo-provera on weight. Given the fact that Depo-Provera either increases or decreases weight, changes in mean values may not be the appropriate measure to assess effects. Women gaining weight and those losing weight should be treated as two separate groups manifesting two different pathological effects of the drug.

The increase in weight experienced by women on Depo-Provera could be due to its glucocorticoid-like activity (Schwallie & Assenzo, 1973). Increased appetite has been postulated as another possible mechanism (Lande, 1995). No mechanism has been postulated for the observed loss of weight in women on Depo-Provera.

Depo-provera is being advocated as a means of increasing body weight of undernourished women. However, women from poor households do not find weight gain wiht Depo-provera acceptable. Weight gain was responsible for 24 % of the discontinuers in a report from a relatively low income group attending health facilities in New York city (Polaneczky et al., 1996).

Food and exercise diaries, as well as a review of healthy food choices have been suggested as methods which can help women on Depo-Provera to manage their weight (Polaneczky et al., 1996; Anon, 1997).

7. Depo-Provera and Galactorrhoea

Several studies report the presence of galactorrhoea in women on Depo-Provera.

In a study of a small sample of 14 women on Depo-Provera contraception for a minimum of 1.2 years, 2 women presented with galactorrhoea and slightly elevated serum prolactin levels of 23 and 29 ng/ml (the normal range in that laboratory being 3 to 19 ng/ml) (Garza-Flores *et al.*, 1985). In these women, prolactin levels became normal and the ovarian function was re-established by 18 months.

In a clinic based study, galactorrhoea was observed in 64% of women using Depo-Provera (n=97) as compared with 15% of women (n=40) using IUD (p<0.001) (Gongsakdi & Rojanasakul, 1986). Serum prolactin levels in Depo-Provera group varied from 1 to 46 ng/ml and 18.6% of women (18/97) from the Depo-Provera group had serum prolactin levels of more than 20 ng/ml. Of this, 14 women had galactorrhoea on physical examination. The serum prolactin levels of only the Depo-Provera users were measured.

The mean serum prolactin level was only slightly higher in the galactorrhoea group as compared with the non-galactorrhoea group of the Depo-Provera users but the diffference was not significant (15.19 ± 8.34 vs 14.3 ± 6.45). The wide confidence interval indicates the inadequacy of the sample size. A subsample of the Depo-Provera group (n=36) and IUD group (n=4) who had galactorrhoea were subjected to a radiological study of the sella turcica which did not reveal any abnormality. The authors have however advised yearly determination of prolactin level in Depo-Provera users with galactorrhoea. There are several limitations in both methodology (clinic based) and analysis of the data (not

controlled for confounding variables) in this study and there is need for further studies to examine association.

Galactorrhoea was reported by 9% of teenagers (n=64) who received Depo-Provera at the adolescent clinic at Yale-New Haven (Connecticut, USA) hospital between 1984 and 1992 (Cromwell & Anyan, 1998). There was no correlation between the onset of galactorrhoea and timing of the first injection of Depo-Provera or the duration of use. All 6 women had negative serum human chorionic gonadotrophin assays and the serum prolactin concentration was under 20ng/ml. 5 women had spontaneous symptom resolution within several months while the 6th woman's galactorrhea persisted for 18 months. The authors suggest that the galactorrhoea could be the direct result of Depo-Provera on the breast tissue.

Galactorrhoea in association with menstrual disorders are the most common manifestations of hyperprolactinemia (Copeland, 1993) (see box). However, the more important concern is the possibility of pituitary adenomas and tumors[14]. In this context the "warning" in Upjohn drug literature assumes a grave significance.

"Warning.......

5. *Ocular Disorders*[15]

Medication should not be readministered pending examination if there is a sudden partial or complete loss of vision or if there is a sudden onset of proptosis, diplopia, or migraine. If examination reveals papilledema or retinal vascular lesions, medication should not be readministered."

(Upjohn, 1993).

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14. Progestogens are known to cause pituitary adenoma in animal models. In 1971, NET-EN was withdrawn from the market because of pituitary and liver nodules in rats.

15. These effects should not be classified under "ocular" disorders.

"Hyperprolactinemia is a biochemical result not a diagnosis. It is defined as a persistently elevated serum prolactin levels in a non-pregnant, non-lactating, women or in a child or any male.

Although menstrual disorders and galactorrhea are the most comman manifestations of hyperprolactinemia, there are other concerns. Headaches are out of proportion to the presence of pituitary tumor. They are usually frontal and are reported as penetrating behind the eyes. the presence of headaches should suggest a search for an underlying pituitary tumor. Superior extension to hypothalamus may result in disorders of body weight, sleeping pattern and core body temperature....

Hypoestrogenization may result in symptoms of decreased libido, dyspareunia, and vaginitis, mild hirusutism, acne and seborrhoea have been noted in some women with hyperprolactinemia..... superior extension may give chiasmal compression and thus peripheral visual loss and even papilledema" (Text book of Gynecology, Copeland, 1993)

8. Depo-Provera and cancer risk

*"**Warnings***

Cancer Risks

Long-term case-controlled surveillance of users of DEPO-PROVERA Contraceptive Injection found slight or no increased overall risk of breast cancer and no overall increased risk of ovarian, liver, or cervical cancer and a prolonged, protective effect of reducing the risk of endometrial cancer in the population of users".

(Uphohn Co., 1993)

In 1979, the World Health Organization (WHO) special programme of Research, Development, and Research Training in Human Reproduction, launched a multinational collaborative case-control study to examine the relationship between steroid contraceptives and the risk of selected neoplasms (WHO, 1986). With reference to Depo-Provera, the study examined the risk of breast, cervical, endometrial and liver cancers and was carried out in five centres from three countries viz., Kenya, Mexico and Thailand (three of the centres were from Thailand).

In October 1992, following the publication of the final results of the study, especially that related to breast cancer, the United States Food and Drug Administration (USFDA) granted approval to the Upjohn Co. for the marketing of Depo-Provera contraceptive and the Indian government in its turn approved the introduction of Depo-Provera in the private sector.

This review will focus on Depo-Provera and the risk of breast and cervical cancer because the former study was instrumental in getting the approval of the USFDA and the latter (cervical cancer), is a cancer of public health importance in India.

8.1. The WHO's study on Depo-Provera and breast cancer

Between October 1979 and September 1988, a total of 962 cases and 12,319 controls were recruited from the five centres. Cases included all women diagnosed by a local pathologist as having a malignant breast tumour whose date of birth indicated that they could have been at risk of exposure to Depo (i.e., those born after 1924 in Chiang Mai and after 1929 in the other centres), and who were resident of a defined geographic area served by the hospital during the preceding year.

For controls, in addition to the above two criteria, selection was from women admitted to the hospital for conditions unrelated to contraceptive use. 30% of the controls had been admitted for diseases of the digestive system and the remainder for diseases in fifteen other major groups.

A standardized questionnaire was administered by trained female interviewers and confirmation of diagnosis and uniform histological classification was through a reference pathologist. The final analysis included 869 cases and 11,890 controls.

12.5% of the cases and 12.2% of the controls had ever used Depo-Provera and the overall relative risk of breast cancer in ever users, adjusted for age, centre, and age at first live birth, was 1.21 (95% CI, 0.96,1.52). The relative risk (RR) of breast cancer in the study population from the three Thai centres was 1.26 with the lower limit of the 95% CI just below unity (0.99, 1.60). In the analysis the results from all the five centres had been pooled together because the variation between the centres was not significant.

In women aged less than 35 years, the relative risk estimates were more than 1.0 irrespective of duration of use but there was no trend of increasing risk with months of exposure. Relative risk was greater than 1.0 in women in all age groups who used Depo-Provera for less than 3 months, the overall risk in this sub-group of women was 1.67 (95% CI, 1.07, 2.6) which was statistically significant.

There was a doubling of risk in women in all age groups first exposed within the previous 48 months (RR 2.02; 95% CI, 1.35,3.01)

and the risk was greatest in women under 35 years of age who were first exposed to Depo-Provera in the previous 48 months (RR 2.19; 95% CI 1.23, 3.89). In these three groups, the 95% CI does not include 1 and therefore these results are statistically significant.

Heightened surveillance for breast cancer in users of Depo-Provera, a possible source of bias which could explain the anomalous finding, was ruled out on the basis that there was no indication that women with "features of use associated with an increased risk of breast cancer were diagnosed with smaller, less advanced tumours than other women" (WHO, 1991).

The report of the study ends on a convoluted note that these results provide "some assurance that women who have used DMPA for a long time and who initiated use many years previously are not at increased risk of breast cancer" (WHO, 1991). However, before we accept these conclusions as "reassuring", certain methodological problems need to be addressed.

Ascertainment of exposure

In this study, exposure to Depo-Provera was ascertained through interviews and to facilitate recall of time of use and products taken, a calendar and samples of locally available contraceptives were used. Where available, information obtained through interviews was supplemented from medical records of women with a history of Depo use. Further, duration of each period of continuous use of Depo was calculated by adding 3 to the number of months between the first and last injection for women who received injections every three months and 6 for those who received injections every 6 months and the lifetime exposure was calculated by adding numbers of months in each period of use.

The study does not mention the proportion of women whose exposure status was available from medical records and the proportion of women who had to rely on memory recall. (The fact that this has not been mentioned leads one to suspect that the proportion relying on memory recall was probably large). We are therefore not in a position to know the percentage of women who had to rely on

memory recall for the specific preparation of the injectable they were given, the dose and the total duration of exposure and especially if there were breaks in exposure due to an intervening pregnancy or other reasons.

The three centres in Thailand provided approximately 80% of the cases and controls in the WHO study. Depo-Provera was introduced into Chiang Mai, Thailand, in 1965. Since then, in this province of Thailand, apart from the regular recommended dose of 150 mg three monthly, several other regimes of Depo have been tried out at various points in time, viz., Depo given every three months followed by every 6 months (McDaniel, 1968), 400 mg every 6 months (McDaniel & Pardthaisong, 1974), 450 mg every 6 months (Pardthaisong *et al.*, 1988), and 300 mg every 6 months (Pardthaisong & Gray, 1991).

The community-based family planning services of the Population and Community Development Association, Bangkok, which covered more than 1/3rd of all villages in Thailand at that time offered both Depo-Provera and another injectable contraceptive Noristerat[R] (Norethisterone enanthate or NET-EN) to potential users (Viravaidya *et al.*, 1982). NET-EN was registered and commercially available in Thailand around 1981 (Monsereenusorn, 1982). There is also a report that in the early eighties a local brand of DMPA 'Pheno-M' was available in Thailand (Pardthaisong, 1987).

Thus from the published literature, one gathers that between 1965 and 1988, Depo-Provera as a contraceptive was available in several doses and regimens, NET-EN was available, probably, in two schedules (bimonthly for the initial 4 injections followed by every 3 months; and a regular 60 day ± 14 day schedule) and there were other local brands.

We do not know if in Thailand all these injectable contraceptives were prescription products or if they were sold as over-the-counter drugs as part of the 'social inundation' programme. If the situation in Thailand is anything similar to that in India with almost all the drugs, including the injectable contraceptives, being sold over-the-counter without prescription, the possibility exists that the same

woman may have taken different preparations of injectables at different times.

This may have also occurred in community health programmes whenever there was a shortage with a particular preparation as is seen in other developing countries (ICDDR, 1992). Moreover, it has also been reported that in Thailand especially in the Chiang Mai area, pregnant women have been known to take Depo-provera in the mistaken belief that it is an abortifacient (Pardthaisong, 1991). In such cases the woman may not admit to use for this 'non-approved' use.

In Family Planning Programmes in Third World countries, health workers have little time or inclination to explain to women which brand or which dosage they are being given. It is more likely that all these preparations would have been known only by their 'generic' term — injectable contraceptive.

In the three centres in Thailand, women were recruited from between October 1979 and September 1988 i.e., for a period of 9 years. For a woman who was administered Depo-Provera in 1965 in Chiang Mai and who developed breast cancer and therefore became a case in 1988, the recall period would be close to 23 years; for a woman who was administered Depo-Provera in the last "48 months" of developing breast cancer, the maximum recall period would be 48 months and hence women recruited in the study may have differential recall of events due to the passage of time.

Moreover, once the study was initiated in 1979, it is likely that for the 9 years of the study, the centres may have taken special efforts to maintain better records of DMPA users with the resultant improvement in the quality of information for this period. Thus, the quality of information on exposure status may not have been uniform throughout the study period.

Being largely rural and non-literate, it is unlikely that the women in the WHO study would have been in a position to give accurate history of exposure. The long period of recall between exposure and the diagnosis of the disease would have added to the inaccuracies. Although, the authors of the study state that a calendar and locally

available contraceptives were used to facilitate memory recall, there is no indication in the report whether the validity and reliability of these instruments were evaluated.

Studies comparing women's responses to questions concerning use of oral contraceptives and prescriber's records in the literate western world has shown that recall of details of past use, such as different formulations, different brands, breaks in usage, starting and stopping dates, deteriorates with the passage of time (Stolley *et al.*, 1978).

Random misclassification of exposure due to these biases could then result in an underestimation of risk which would shift the relative risk towards unity.

Exclusion criteria for cases and controls

According to the original study design (WHO, 1986), in order to eliminate surveillance bias, cases and controls referred from fertility or family planning clinics were to be excluded unless the visit leading to hospital referral was the woman's first visit to the fertility or family planning clinic. This decision had been taken to prevent over-representation in the study of cases that had used steroid contraceptives. The investigators were also aware that this criteria of exclusion could have a potential to create bias and have a reverse effect. If women attending the fertility or family planning clinics were more likely to be using Depo-Provera and if the cancers were more likely to be diagnosed in these clinics than other conditions leading to hospitalization, exclusion of cases from these centres would have meant an under-representation of cases with history of Depo-Provera use.

The report on the cancer study does not indicate if this exclusion criteria was observed and if so, how many cases and controls were excluded because of this criteria.

Interviewer's bias

Internationally, the potential association between Depo-Provera and breast cancer was one of the most publicised controversies in

contraceptive research. It is unlikely that in the WHO study it would have been possible to keep the interviewer blind either to the hypothesis to be tested or case/control status of the study population. Chiang Mai is also the province where Depo-provera was introduced by McDaniel of McCormick hospital as a regular contraceptive even before the Upjohn Company had submitted the new drug application to the USFDA for approval as a contraceptive (McDaniel, 1968). Given this, the enthusiasm for Depo-Provera may have led to the differential probing of control and cases for history of exposure.

Moreover the WHO, the coordinating agency for the study had recommended the use of Depo-Provera as a safe contraceptive even before the preliminary results of this study were available (WHO, 1982) indicating a conflict of interest.

Latent effects in the interpretation of cancer studies

In a critique of interpretation of association between oral contraceptives (OCs) and breast cancer, McPherson (1991) has pointed out that epidemiological studies are generally interpreted on the assumption that the possible causative mechanisms that are being investigated have immediate effect. However, for many chronic diseases such as cancer, time delays between exposure to risk factors and diagnosis of disease can sometimes be as long as several decades. This latent period includes an induction period when the first cancer cell is evolving and a pre-clinical period which is the time interval between induction and the clinical diagnosis of cancer. Based on the natural history of breast cancer, it has been estimated that the latent interval could be 30 years or more.

Although Depo-Provera was introduced into Chiang Mai in 1965, the Ministry of Public Health of the Government of Thailand 'approved' its use only in 1975. This could mean a low prevalence of use between 1965 to 1970, a moderate prevalence between 1970 to 1975 and perhaps a higher prevalence after that.

In the WHO study, among the women in the study population, 76% of the cases and 78% of the controls had reported "months since first use" of DMPA as being less than 13 years. Thus, one of the major

limitation of this study is that sufficient time period has not elapsed between exposure and the study period to account for a latent period of 20 to 30 years.

According to McPherson (1991) there is a necessary association between exposure to OCs at a young age and being currently young and that one of the conflicting findings of the several studies carried out to examine the association between OCs and breast cancer could be attributed to differences in time at which early use became common among young women. Studies of this association will lack precision if the latent period is more than 20 to 30 years because relevant exposure sufficiently long ago may be currently rare.

This could very well be the explanation for the overall negative results of the WHO study on Depo-Provera and breast cancer. The timing of the study could have meant that proportionately less than adequate number of women in the younger age groups may have been exposed sufficiently long ago. One of the criteria in the WHO study pertaining to the age of the women as a cut off point was that only women born after 1924 in Chiang Mai and after 1929 in the other centres were to be included to ensure risk of exposure to Depo-Provera. Only women aged less than 35 years of age at the time of diagnosis would have been exposed to Depo-Provera when sufficiently young and in the study on breast cancer only 1 case and 13 controls in this age group had been exposed to Depo-Provera, 13 years earlier to recruitment into the study.

The WHO's study on Depo-Provera and the risk of breast cancer has several methodological problems. The possibility of a high degree of random misclassification of exposure and a consequent under estimation of risk could very well be the explanation for a lack of overall association between cancer breast and Depo-Provera observed in this study. Given the possibility of random misclassification, the finding of a doubling of risk in young women with a history of recent use of Depo-provera while a true risk is probably an under estimation of the real risk. The WHO study is also not in a position to assess the delayed effects since sufficient time has not elapsed

between the widespread use of Depo-Provera and the development of disease.

Evidence from other studies

Evidence from two other case control studies have also corroborated the positive findings of the WHO study.

In Costa Rica, 171 women aged between 25-58 years with breast cancer diagnosed between 1982 and 1984 (cases) were compared with 826 women (controls) randomly chosen during a nationwide household survey (Lee *et al.*, 1987). 33.2% of the eligible breast cancer cases from the cancer registry could not be interviewed, death being the major reason. Results were adjusted for age, parity and socio-economic status. Depo-Povera users had an elevated relative risk of 2.6 (95% CI, 1.4,4.7) compared with never users. Women who had used Depo-Provera for less than 12 months also had an elevated risk of relative risk of 2.3 (95% CI, 1.0,5.1). The dose response could not be ascertained because of the small numbers. The relative risk of breast cancer associated with Depo-Provera use was highest for women who had the longest time i.e., ten or more than ten years, since first use (RR 4.0; 95% CI, 1.5-10.3). The failure to interview 33% of the eligible cases, possible differential detection of tumors according to Depo-Provera use and misclassification of exposure have been put forward as a likely explanation for the elevated risks.

Another population based case-control study has also found a positive association between breast cancer and Depo-Provera use. In New Zealand, 891 women between the ages of 25 and 54 with newly diagnosed breast cancer (cases) were compared with 1864 women (controls) selected randomly from the electoral rolls (Paul *et al.*, 1989). Overall there was no association between use of Depo-Provera and breast cancer (RR 1.0; 95% CI, 0.80,1.3). However, subgroups of women showed an elevated risk. In women aged 25 to 34, the relative risk was 2.0 (95% CI, 1.0,3.8) and the highest risk was in women who had used it for six years or longer (RR 3.7; 95% CI, 0.63,21.5). In this age group, the trend in risk with duration of

use (dose response) was significant (p<0.001). Relative risk was also elevated in women who had used it for two or more years before 25 years of age and before the first full term pregnancy (RR 4.6; 95% CI, 1.4,15.1). The trend in risk with duration of use was significant (p=0.03).

The data from the WHO study (1991) and the New Zealand study (Paul et al., 1989) when pooled together .did not find any overall association between Depo-Provera and breast cancer (RR 1.1; 95% CI,0.97-1.4) (Skegg et al., 1994). However, the analysis confirmed the findings that there was a significant doubling of risk in women reporting recent or current use, the highest risk was among those who had received only one injection (RR 3.1; 95% CI, 1.8-5.2).

> *"If these results (tripling of risk of breast cancer among women who had received only one injection of Depo-Provera) are accepted as reliable, they lead to the conclusion that a single injection of DMPA suffices to exert the full effect of the hormone on the clinical expression of breast cancer. This is plausible since a single injection of DMPA exerts a potent progestogenic effect extending over a period of several months"* (WHO, 1995).

Increased risk of breast cancer in young women

The doubling of risk in young women using Depo-Provera contraceptive, is a cause for concern especially in countries where breast cancer is a public health problem.

The patho-physiological rationale put forward by WHO for the doubling of risk in younger women is that Depo-Provera could accelerate proliferation of either initiated or fully transformed cancer cell in the breast. Stimulation of initiated cells would promote development of new tumours that otherwise may not develop while the stimulation of existing cancer cells would accelerate tumour growth and result in appearance of breast cancer earlier in users than in non-users. Either of these processes would

result in an increased risk of breast cancer soon after use of Depo-Provera. The authors of the study are more in favour of the tumour acceleration hypothesis, although the other possibility cannot be ruled out since the study lacks adequate power.

If the doubling of risk of breast cancer in young women who reported use within the previous 48 months is due to tumour acceleration, then this is precisely what the much maligned beagle dog studies (WHO, 1982) were all about. In the 7-year toxicological testing of Depo-Provera in beagle dogs, all the dogs that lived beyond the first few years developed mammary nodules which appeared earlier, grew bigger and persisted throughout their lives in comparison to the controls. Although this finding had raised the possibility of increased risk of breast cancer in women as far back as 1979, the finding was dismissed as being irrelevant to women. The explanation put forward was that the breasts of healthy beagles contain a reservoir of microscopic neoplasms which may grow and occasionally become malignant especially in response to prolonged over-stimulation by progestogens and that in contrast such a reservoir had not been seen in healthy women. The findings in the WHO study should now rightly lead to the reopening of the Pandora's box on the suitability of animal models in contraceptive research.

Another explanation put forward for the increased risk is that the effects of Depo-Provera on breast cancer are analogus to those of pregnancy (WHO, 1995). This is on the basis that a short-term increase in the risk of breast cancer has been described following both full term pregnancy and pregnancy terminated by abortion at three months. If this were indeed true, then Depo-Provera should be contraindicated in the postpartum and post-abortion period.

The tumour acceleration effect of Depo-Provera has serious implication in populations where breast cancer is a problem of public health importance because of the subsequent shortening of life span in women who use the contraceptive. In this context, the recent attempts by the WHO (1992) and the United States Agency for International Development (USAID) (Shelton & Calla, 1991) to arrive at an international consensus regarding the waiving of breast

and pelvic examination as a part of contraceptive service in Family Planning clinics is to be viewed with disquiet.

Given the fact that currently, no simple or cheap technology exists to detect the presence of occult breast cancer in women who are to be given Depo-Provera, use of Depo-Provera as a contrapective in young women needs to be questioned.

> ### Small comfort this !
>
> *"If women had not developed breast cancer within five years after starting DMPA, they faced no increased risk"*
>
> (Lande, 1995).

8.2. Depo-Provera and the risk of cervical cancer

The WHO's multinational collaborative study of neoplasia and steroid contraceptives (1986) also assessed the potential risk of cervical cancer, both invasive cancer (1992) and carcinoma *in situ* (1995) with Depo-Provera.[16]

Risk of cervical carcinoma

In the 2009 cases of cervical cancer and 9583 controls selected from the five centres, the relative risk of invasive squamous cell cancer of the cervix (adjusted for age, total number of pregnancies, number of prior pap smears, previous use of oral contraceptives and centre), in Depo-Provera users was 1.1 (95% CI, 0.96,1.29) (WHO, 1992).

The relative risk estimates of invasive cervical cancer showed a 24% increase in risk in women aged less than 35 years (RR 1.24; 95% CI, 0.97,1.6); and 21% increase in women between the ages of 36 and 45 (RR 1.21; 95% CI 0.99, 1.50) with the lower limit of the 95% CI in both being just below unity.

The relative risk were highest in women who were first exposed to Depo-Provera before the age of 25 years (RR 1.28; 95% CI, 0.96,1.70) and declined with increasing age at first use, although the

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16. This study is subject to all the limitations of the methodology, particularly that pertaining to exposure ascertainment and random misclassification, discussed under Depo-Provera and breast cancer (p 69-73).

trend was not significant.

According to the authors, a surprising and apparently inexplicable finding in this study was that the relative risk in women who had ever used Depo-Provera and had a single sexual partner was 1.25 (95% CI 1.06, 1.48) compared to an estimate of 0.82 (95% CI, 0.63, 1.06) in women with more than one partner (difference between the two groups, statistically significant, p = 0.005). The investigators contend that an explanation for the observed risk was not readily apparent.

Another large multinational case-control study from four areas of Latin America (Costa Rica, Panama, Mexico City and Bogota, Columbia) with 759 cases and 1430 controls reported no overall association of cervical cancer with depo-Provera (Herreo *et al.*, 1990). However, the relative risk was directly related to duration of use and was significantly elevated in women who reported a duration of use of five years or more (RR 2.4; 95% CI, 1.0-5.7). This increased risk persisted after adjusting for confounding variables and when analysis was restricted to women with a single partner. The relative risk was higher for longer periods since the first and the last use.

The findings of these two large multinational studies suggest a possible risk of association of cervical cancer with Depo-Provera. Yet, the WHO study concluded that the results provided reassurance that "prolonged use of Depo-Provera does not enhance the risk of invasive squamous cell cervical carcinomas, even after a potential latent period of over a decade" (WHO, 1992). However, given the several methodological limitations, especially with the WHO study, the overall conclusion of the study should not be considered unequivocal.The moderately increased risk of cervical cancer with Depo-Provera is found to be biologically plausible on the evidence of association between oral contraceptive and cancer cervix (Vecchia, 1994).

Risk of Carcinoma *in situ*

The WHO study on carcinoma in situ and Depo-Provera was restricted to data from three hospitals in Thailand and one from

Mexico[17] (Thomas, 1995). A total of 1372 cases and 11,888 controls accrued from the four centres; of this, 1225 cases (89.3%) and 11,299 controls (95.0%) were interviewed. After exclusion, in the analysis a total of 1217 newly detected cases of carcinoma *in situ* were compared with 8956 controls. The histological confirmation was by reference pathologists who were blind to the woman's contraceptive history.

Women with carcinoma *in situ* were more likely than controls to have ever used Depo-Provera (23.3% vs 15.4%). the overall relative risk (adjusted for age, number of pregnancies, pap smear, frequency and ever use of oral ontraceptives) was 1.43 (95% CI, 1.22, 1.67). Ever users of Depo-Provera who had no symptoms at diagnosis had almost a doubling of risk (RR 1.92; 95%CI, 1.51, 2.44; p<0.05). To rule out screening bias, the analysis was restricted to women with symptoms. The relative risk in this sub group was 1.25 (95% CI, 1.02, 1.52). The relative risk increased with duration of use and the trend test for women in this subgroup was significant (p = 0.017). Asymptomatic women who had used Depo-Provera for five years had a three fold increase in risk of carcinoma *in situ* (RR 3.07, 95% CI, 1.93, 4.87).

A prospective study from New Zealand however did not show any association between Depo-Provera and cervical cancer (New Zealand Contraceptive and Health Study Group, 1994a). Three cohorts of women aged 20 to 39 attending medical practitioners' or family planning clinics in New Zealand for contraceptive advice were followed prospectively for five years. The three cohorts were defined by prescription of either of the three methods: OC (n=2469), IUD (n=2072), or Depo-Provera (n=1721). Follow up was to be annual and included a cervical smear. A positive outcome, 'dysplasia' was any degree of definite dysplasia or carcinoma of the cervix diagnosed cytologically by a central study laboratory and

17. Although the cervical cancer portion of this study was conducted in several countries, only data from three hospitals in Thailand and one in Mexico were utilized for this report, because only in these areas there were sufficient numbers of cases of Carcinoma *in situ* and women exposed to Depo for meaningful analysis (Thomas, 1995).

confirmed by histology or analysis of DNA ploidy. In the three cohorts, 12839; 10774; and 8984 person years of follow up accrued and there were 125; 92; and 101 cases of confirmed dysplasia in the three cohorts (OC, IUD and Depo-Provera respectively). The crude rate of dysplasia per 1000 person years was 9.6 in the OCs, 8.4 in the IUD and 11.3 in the Depo-Provera group. The increased rate of dysplasia with Depo-Provera, however, disappeared on controlling for potentially confounding variables. One of the limitation in this study was that the 1721 Depo users had an average of 2.4 years of use median (2.1 years) of the drug, too short a period of use.

A case-control study nested in the cohort study was therefore designed to overcome this (New Zealand Contraception and Health Study Group, 1994b). Duration of use was based on retrospective recall of the woman. The cumulative incidence of risks of confirmed dysplasia was higher in Depo-Provera users, the age-adjusted incidence risk in the category of 4 years of use or more was higher than 50% in Depo users and these occurred solely among women less than 35 years of age. (Regression coefficient for 4 years use in age group 20-24, 0.34; 95% CI,-0.80, 0.09; p=0.07). The study concluded that though there was a modest increase in risk of cervical dysplasia among Depo-Provera users in New Zealand, it was entirely attributable to the characteristics of women who choose the injectable for contraception (intercourse at early age, multiple sex partners and smoking).

> *"The evidence from the two most recent studies that young women exposed to DMPA may have an increased risk of breast cancer, is cause for concern for the same reasons that oral contraceptives are cause for concern: that breast cancer is a major problem in the developed world and that even a small increase in breast risk in women diagnosed before age 35 would be a major potential public health problem if that risk persisted past the menopause. To look at breast cancer in isolation, is, however, a failure of perspective. Moreover, the total health cost-benefit equation will differ between developed and developing countries partly because background breast cancer rates differ, but also because the consequences of unwanted pregnancy, in terms of maternal morbidity and mortality, are so different"* (Chilvers, 1994).

9. Return of Fertility

"If you wish to have a child

Because Depo-Provera is long-acting, it takes some time after the last injection to wear off. This time varies from woman to woman. Most women must expect to wait at least 6-8 months after the injection to be able to become pregnant. In rare cases, it can take two years or longer. This delay in being able to become pregnant after stopping Depo-Provera is not related to the length of the treatment."

(Upjohn, May 1992).

Depo-Provera is being offered as a temporary, spacing method of contraception. One of the important characteristics of a spacing method is that when the woman discontinues the method, her fertility should not be impaired as a consequence of taking the contraceptive. As would be expected, condoms and diaphragms have the least effect on future fertility once the method is discontinued.

Return of fertility following discontinuation

In assessing return of fertility, return of menstruation, return of ovulation, and conception rates are taken as markers.

14 Mexican women who had received Depo-Provera for a minimum of 1.2 years were recruited in a study after 90 days of the last injection (Garza-Flores *et al.*, 1985). The mean time of resumption of menstruation in these women was 4.3 ± 2.2 months, 90 days following the last injection; and the return of ovulation as established by the serum levels of progesterone (i.e., > 5ng/ml) was 5.5 ± 1.9 months. Till the end of the one year follow-up period, 4 of the

women (28.5%) had not ovulated. In two of the women who had presented with galactorrhoea and elevated serum prolactin levels, the first menstrual bleeding was at 6 months but the ovarian function was re-established only around 18 months after the expected effect of the last dose i.e., 21 months after the last injection. Return of menstruation and return of ovulation may thus not be simultaneous or concurrent.

A retrospective analysis of data of women attending a gynaecological practice in Melbourne, Australia, since 1973 showed that of 363 women receiving 2298 injections in the last 20 year, 80% had received it for contraceptive purposes. The median delay in conception for those wishing to conceive was 9.2 months (Fraser & Dennerstein, 1994)

Two epidemiological studies have reported on pregnancy rates following discontinuation with Depo-Provera.

Upjohn's study on American women

The drug literature of Upjohn Co. (1993) refers, without giving any citation, to a "large" American study on women who discontinued use of Depo-Provera to become pregnant. According to the brochure, "based on Life-Table analysis of these data, it is expected that 68% of women who do become pregnant may conceive within 12 months, 83% may conceive within 15 months, and 93% may conceive within 18 months of the last injection" (i.e., 9 months, 12 months and 15 months after the expected effect of the last dose).

This study, carried out by the Fertility Research and Biostatistics Division of the Upjohn Co., Kalamazoo, is based on the 'large' sample of 188 women who had discontinued Depo-Provera to become pregnant (Schwallie & Assenzo, 1974). Of the original cohort, 39.4% dropped out and no data is available on their pregnancy status. In the remaining 60.6% of the original cohort of women who were followed up, the median time to conception, after the period of expected effect of the last dose was 7 months whereas with IUD, diaphragm, or condom, the median time to conception after discontinuation was 2 months. Thus compared to

these methods, there was a considerable delay in return of fertility in Depo-Provera users.

In this study, the cumulative conception rate at 15 months for Depo-Provera was 82.8% (95% CI, 75.8, 89.8). While the wide confidence interval shows the inadequacy of the sample size, the lower limit of the confidence interval indicates that the proportion of women not conceiving at the end of one year following the period of 'expected effect of the dose' could be as high as 25%.

Apart from the inadequate sample size, the major flaw in the study, as admitted by the authors themselves is that the "strongest assumption that is being made in the analysis of the Depo-Provera data is that the withdrawals and losses (39.4% of the patients who dropped to become pregnant) would behave in a similar fashion as those who became pregnant. We simply do not know what happened to those who were lost to follow up [49 (26.1%) of the 188]" (Schwallie & Assenzo, 1974).

Epidemiological study from Thailand

The only other study on women who discontinued Depo-Provera to become pregnant, was carried out in Thailand in 1976 (Pardthaisong et al., 1980). The study compared the conception rates in 796 ex-Depo users, 437 ex-oral contraceptive (pill) users and 125 ex-IUD users (Pardthaisong, 1982).

The median conception rate in ex-Depo users was 5.5 months plus 15 weeks to account for the efficacy of the last injection; for ex-pill users it was 3 months and that for ex-IUD users it was 4.5 months. The proportion of women standardised for age who had not conceived at the end of 24 months was 8.5% (SE, 1.01) for ex-Depo users; 5.1 (SE, 0.94) for ex-pill users; and 6.7% (SE, 2.82) for ex-IUD users (Pardthaisong, 1982). At 24 months (often taken as an indication of possible sterility) the difference between ex-Depo users and ex-pill users was statistically significant at 5% level (Pardthaisong, 1984).

In ex-Depo users, there was a greater delay in the conceptions of women over the age of 30 years. The median delay to conception in

this age group was 8.0 months compared to the delay of 5.0 months in the 20 to 24 age group. 14.7% of this sub-group was still not pregnant at the end of 48 months of discontinuation.

On the face of it, the ex-Depo users, although showing a delay in median conception rates, did not seem to be vastly different from ex-IUD users since conception rates were similar in both the groups by the end of nine months of discontinuation. This has led the author to conclude that Depo-Provera does not cause long-term impairment of fertility relative to the IUD. However, a critical examination of the study design raises questions about the validity of their conclusion.

In this study, women who discontinued contraception between 1965 and 1976 for the stated reason of planning pregnancy were recruited in 1976 (Pardthaisong et al., 1980). Of the 1448 ex-Depo users, and 422 ex-IUD users identified through hospital records, 447 ex-Depo users and 171 ex-IUD users were excluded because of the subsequent use of other contraceptive methods. In the remaining 1001 ex-Depo users, and 251 ex-IUD users, 205 (25.1%) ex-Depo users and 125 (50%) ex-IUD users were lost to follow up or refused to participate in the study. There is no information on the number of ex-pill users lost to follow up.

Data was collected both retrospectively and prospectively in ex-Depo users. In IUD users, information was collected only retrospectively. In ex-Depo users, 429 women who had discontinued before December 1974 were followed up in 1976; 367 women who had discontinued Depo between January 1975 to December 1976 were followed up from the time of their discontinuation. In the pre-Dec. 1974 group of ex-Depo users (i.e., for the period between 1965 and 1974), and all the IUD users, the conception rate in the years following discontinuation was ascertained on the basis of history. In the 367 ex-Depo women, in the period following 1976, history was taken through a regular 3-monthly follow up. Conceptions in this group was confirmed with a pregnancy test. The follow-up period for all the groups was till August 1977.

Both these studies, the only two studies on large samples published

so far, have serious limitations. In the Upjohn study, there was a 39.4% drop out rate from the original cohort of those who discontinued to become pregnant; in the study carried out by Pardthaisong and colleagues, only 55% of the original cohort of women discontinuing Depo-Provera to become pregnant formed the final sample.

In the study by Pardthaisong and colleagues, the method of ascertainment of pregnancy was not uniform throughout the study period and among the different groups. Moreover, in the majority an imprecise form of ascertainment through history and recall were resorted to. The study also has unacceptably high drop out rates in both the groups and the drop out rate in the ex-IUD group was double that in the ex-Depo users.

The high drop-out rate and loss to follow up could bias the study results because the probability of loss may be related to exposure, outcome or both. Furthermore, those who agree to participate in a study are likely to differ from those who refuse in a number of ways which could include their risk factor status. Moreover, neither of the studies have controlled for potential confounding variables.

Return of fertility in Indian women

The return of fertility following discontinuation of Depo-Provera has not been studied in Indian women. There is however one small study on conception rates following discontinuation of NET-EN in Indian women (ICMR, 1986). The study carried out by the ICMR followed up 230 women who had discontinued NET-EN, 69 for planning pregnancy, 51 because of amenorrhoea, 68 because of excessive bleeding and 42 for personal reasons. The average duration of NET-EN use in women planning pregnancy was 11.9 ($\pm$ 4.9) months. The control group was 110 ex-CuT users with an average duration of use of 28.2 months ($\pm$14.7). The median time for conception in ex-NET EN users planning pregnancy was 7.8 months compared with the median time of conception of 3.7 months in 158 ex-CuT users. The cumulative conception rate at the end of the 12 months was 72.5 in ex-NET-EN group compared with 83.6% in ex-CuT users.

The major limitation of the study was that the ex-NET EN group consisted of women who received NET-EN 200 mg either two monthly or three monthly. NET-EN 200 mg three monthly had been rejected as a contraceptive because of the unacceptably high failure rate of 6.0/100 users at 24 months in Phase III clinical trial (ICMR, 1984). In the study on return of fertility by including the three monthly group, the high failure rate with this dosage was being counted as pregnancy rate after discontinuation. The mean duration of use in the control subjects was double that in the study population which would bias the results in favour of the injectable contraceptive. The analysis did not control for any confounding variables.

The wide variation in time of conception was suggested to be due to wide variability in uptake and metabolism of the injectable.

Return of fertility in sub-groups of women

The return of fertility following Depo-Provera use is not known in important sub groups of the population of users. Clinical studies have shown that bleeding problems and amenorrhoea are the major reasons for discontinuation in Depo users. Both the studies cited above (Pardthaisong, 1984; Schwallie & Assenzo, 1974) have examined conception rates among women who discontinued use with the stated purpose of becoming pregnant. Data has not been presented on conception rates in women who discontinued due to bleeding problems or amenorrhoea.

Women with secondary amenorrhoea due to long acting progestogen preparations have a longer delay in return of fertility as seen from the ICMR study with NET-EN (1986). Women were administered NET-EN and were followed up for one year. In a sub group of 51 women who had discontinued due to amenorrhoea, only 51% conceived within one year. While the sample size is small, the results do indicate that the return of fertility may be unacceptably delayed in this sub-group. The conception rates in the other categories (planning pregnancy, excessive bleeding) were similar to the control group of ex-IUD users.

Depo-Provera is being recommended for nulliparous women and

adolescent girls (WHO, 1990). There are no studies that have examined the return of fertility in these groups. The study carried out by Pardthaisong (1984) mentions that return of fertility was not affected in nulliparous women but this conclusion is based on 35 women, a sample too small to give valid results.

Lactating women who are administered Depo-Provera have been reported to experience a prolongation of amenorrhoea and this is yet another sub-group in which we do not know the status of return of fertility after discontinuation.

Possible causes for a delay in return of fertility

The studies on the return of fertility have reported that the delay is not dependent on the duration of the use of Depo-Provera and that there is no difference in the time taken for return of fertility between long-term and short-term users (Lande, 1995).

Schwallie and Assenzo (1974) of the Upjohn Company state that the mean time to recovery of normal function after discontinuing Depo-Provera (approximately 8 months) corresponds closely to the mean length of time Depo-Provera or its active metabolites are detected in the circulation after a single injection of 150 mg. This would indicate that "prolonged amenorrhoea and anovulation are due to *the presence of active amounts of the drug* rather than inability of the hypothalamus, pituitary, or ovary to recover from the effects of the drug after it has been entirely eliminated". (emphasis supplied).

The levels of Depo-Provera can be detected in the blood 200 days or more after a single injection. The persistence of the drug in blood beyond the 90-day injection interval ensures inhibition of ovulation (WHO, 1982).

If the delay in the return of fertility is due to the persistence of the drug and metabolites in the blood, and not due to accumulation[18]

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18. There is one small study on accumulation of the drug with successive injections with inconclusive results; Koetsawang *et al.*, (1979). Blood levels of medroxyprogesterone acetate after multiple injections of Depo-Provera or cycloprovera. *Contraception*; 20:1.

then what it indicates is the unpredictable pharmacokinetics of the drug. This could be the reason for the unpredictable delay in the return of fertility. Hence, seen in the light of Pardthaisong's study (1984) even if a woman is administered a single injection, her return of fertility could be delayed by more than 24 months.

Reviewing the literature on the pharmacokinetics of Depo-Provera, Mishell (1996) observes that the varying results of studies on the pattern of medroxyprogesterone acetate clearance from the circulation indicates the need for more research to determine the precise pharmacodynamics of the clearance of the drug and the time of the initial resumption of ovulation; women should be advised that it may take as long as a year to clear the drug from the circulation; that the time lag before fertility returns is not related to the number of injections because the half life of the drug is constant; that increased body weight is linked to resumption of ovulation and that ovulation resumes when the blood level of Depo-provera falls below 0.1ng/ml.

If the active drug continues to circulate for more than six months after an injection, a serious implication is that women conceiving during this period will have their fetus exposed to the drug *in utero* for a considerably long period of time.

Irreversible effect on reproductive organs

Prolonged duration of Depo-Provera use could lead to serious and irreversible effects on the reproductive organs.

A study that had examined ovarian tissue from 20 women who had received Depo-Provera for 18 to 20 months showed a difference in ovarian function in women reporting regular bleeding and those with amenorrhoea (El-Mahgoub *et al.*, 1972). Ovarian specimens examined during cycles of acceptable length and duration of flow revealed signs of follicular activity. All stages of follicular development and lutenized cystic follicles were encountered. Mature Graffian follicles were found in two 'specimens. A corpus luteum was detected in one case indicating ovulation. In contrast, the ovarian tissue examined in women with amenorrhoea revealed either com-

plete follicular suppression where only primordial follicles were detected or showed a polycystic pattern. Polycystic ovaries contained multiple non-lutenized follicular cysts of variable size. The cortical tissue was reduced in amount.

As part of a larger study, ovarian specimen[19] from 21 Mexican women on Depo-Provera 150 mg three monthly were compared with 42 normal women (Maqueo *et al.*, 1972). The duration of use in 4 women was less than 6 months, in 10 it was 6 to 12 months and in 7 it was from 1 to 3 years. The majority of the ovaries appeared to be small and seemingly inactive on gross inspection. There was arrest of follicular growth and disturbance of the development of secondary follicles. Tertiary and mature follicles were not seen. Almost all (19 women) had an increase in ovarian connective tissue. Cortical fibrosis was discrete in 8, moderate in 4 and marked in 7 specimens. A large number of atretic follicles and cystic dilatation was seen and in 7 women it resembled that seen in polycystic ovaries. In two women, under treatment for less than 1 year, both ovaries were congested. The cortical fibrosis of the ovaries was not related to the duration of use.

27 Chilean women who had received Depo-Provera in different dosage schedules ranging from 200 mg to 1000 mg and had received 1 to 5 injections underwent surgical exploration (Zantru *et al.*, 1970). In 13 the interval between the last injection and laparotomy was 2 to 6 months and in 14 it was 7 to 14 months. The uterus in both groups was slightly smaller than that expected in a multiparous woman. A substantial wedge biopsy (about 2 cm wide from cortex to medulla) was taken[20]. No significant changes were seen. There was a slight oedema and some condensation of the connective tissue

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19. It is not clear whether informed consent was taken for ovarian biopsy from the Depo users. Study funded by USAID.
20. Again, it is not clear if informed consent was taken from women for the biopsy. This group of women formed an experimental group for the testing of Depo-Provera. 18 women were operated for tubal sterilization and for correction of a 'gynecologic condition'. The reason for laparotomy in the other 9 is not given. Study funded in part by the Ford Foundation.

in the ovarian cortex stroma. However, with the staining method used, no definite fibrosis of the ovarian cortex, albuginea and stroma was found. The authors however, did not rule out the existence of true ovarian fibrosis .

Depo-Provera has also been known to cause endometrial atrophy and a prolonged secondary amenorrhoea due to the drug could be an indication of endometrial atrophy. There are no systematic studies to show whether the endometrial atrophy is reversible or not. (For detailed discussion see section on amenorrhoea).

To a concern expressed in a WHO symposium about the possibility of infertility due to Depo-Provera,

"Baird: As Dr Gray pointed out, the acceptance of amenorrhoea will vary from culture to culture. On the other hand, I should point out that the infertility due to amenorrhoea following injectables or OCs are now emi-nently treatable. Hill et al[21] (1979) have just published data to show that the fertility rate in women treated for infertility associated with amenorrhoea is as good as in the general population. So I wouldn't think that this would be a significant hazard for women who wanted more children" (Diczfalusy, 1980).

To tackle the problem of a drug induced infertility, the answer seems to be to give an equally hazardous ovulation inducing drug[22] .

In sum, so far, studies even with all their limitations, have shown that there is a definite and an unpredictable delay in the time to conception in ex-Depo users who discontinue to become pregnant. Women receiving even a single injection can have a delay of two years or more. In women aged more than 30 years, the delay is much longer. It is not known if there is an accumulation of Depo-Provera

21. Investigation and treatment of amenorrhoea resulting in normal fertility. *BMJ*. 1979;1:1257-51.
22. Use of mentropin therapy to induce ovulation in Depo-Provera users has been recommended (Nelson, 1996).

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with successive doses. In the absence of studies in adolescents[23] and nulliparous women, it may be prudent to withhold use of Depo-Provera as a contraceptive from this group. Prolonged duration of use could also lead to permanent infertility due to irreversible ovarian and endometrial atrophy and fibrosis. In India, the social consequences of infertility are well known.

> *Medroxy Progesterone acetate (Depo-Provera) is injected intra-muscularly in a dose of 150 mg every 3 months (or 450 mg every 6 months) but should be used only if the possibility of permanent infertility is acceptable to the patient. An unpredictable duration of amenorrhoea and anovulation can result from such therapy. Although long-acting preparations of progestins are employed in a number of countries for contraception such use remains investigational in the United States.*
>
> (Goodman & Gilman's, 1991).
>
> (The approval by the USFDA was on the basis of the WHO's multicentric study on Depo and cancer of breast, cervix, endometrium and liver. There has been no new study on return of fertility in the last few years).

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23. Surveys eliciting attitudes of pediatricians, particularly among the Swedish clinicians, involved in adolescent health care showed the "worst fears" with Depo-provera use included infertility (p<0.0001) (Cromer *et al.*, 1993).

10. Depo-Provera and HIV

"Protection against Sexually Transmitted Diseases:

Patient should be counseled that this product(Depo-Provera) does not protect against HIV infection (AIDS) and other sexually transmitted diseases."

(Upjohn Co., 1993)

The increase in risk of transmission of HIV with Depo-Provera could be due to the mode of delivery of the contraceptive which is given as an intramuscular injection. Recently, it has been hypothesised that the use of Depo-Provera can increase vertical transmission of HIV infection by altering the cervical and vaginal mucosa in users.

Depo-provera is administered as an intramuscular injection. Injections given with nonsterile needles or syringes increase the risk of transmission of infectious agents, including bacteria, the hepatitis B virus and the HIV (WHO, 1990).

The WHO Expanded Programme of Immunization (EPI) has estimated that chiledn under five years receive over 5.5 billion injections of all types each year and about half of these injections risk infection of some sort (Lande, 1995). The risk of injection if all providers reused each needle and syringe one time for immunization without sterilizing or disinfecting them has been calculated for different situations. In areas such as the sub-Saharan Africa where the prevalence of hepatitis B is 10%, 260 per 100,000 fully immunized infants would be infected with hepatitis B. In areas with an intermediate prevalence of HIV infection of 1% among

pregnant women, 3 infants and 12 women per 100,000 would be infected with HIV.

The injectable contraceptive is targeted at women in the reproductive age group for the duration of their reproductive span which may be curtailed by the use of a permanent method. In India, there are approximately 41 million women who could be considered 'unprotected' and substantial proportion in need of the injectables. A conservative estimate would suggest about 2000 new cases of HIV infected women added per year if 50% of the women accept the injectable.

Health providers are also at risk of needle stick injury. In a study of immunization, for every 500 injections, there was one needle stick injury. If stuck with a needle used on a client infected with hepatitis B, 5% to 27% of providers become infected (Lande, 1995).

It has been argued that while HIV can be transmitted readily through contaminated intravenous injections, the potential risk from intramuscular injections is low and since HIV can be inactivated at 60°C, it is unlikely to pose a problem either for the user or provider (WHO, 1990). While this may be true in individual practice, administration of the Depo-Provera through the mass family planning programme is likely to increase trasmission of blood borne infections including HIV.

Depo-Provera as an independent risk factor for HIV Transmission

Recent studies are beginning to indicate that Depo-Provera may itself be a risk factor in transmission of HIV and other sexually transmitted diseases. Use of Depo-Provera has been indicted as a factor influencing shedding of HIV-1 infected cells in cervical and vaginal secretions (Mostad et al., 1997). Women attending a municipal STD clinic in Mombasa, Kenya, between December 1994 and April 1996 and who had previously tested positive for HIV-1 were "invited" to take part in the study. Cervical and vaginal secretions from 318 women who were seropositive for HIV-1 were

evaluated for the presence of HIV-1 infected cells. 70% of the women worked in prostitution. HIV infected cells were detected in 51% of endocervical and 14% of vaginal swab specimens. Both cervical and vaginal shedding of HIV-1 infected cells were highly associated with CD4 lymphocyte depletion ($p=0.00001$ and $p=0.003$ respectively). After adjustment with CD4 count, cervical proviral shedding was significantly associated with use of depot medroxyprogesterone acetate (OR 2.9; 95% CI, 1.5, 5.7). The study concluded that use of Depo-Provera may be an important determinant of sexual or vertical transmission of HIV-1.

The authors postulate that the effects of Depo-Provera on the increased cervical and vaginal shedding of HIV-I may be due to direct effect on the virus, effects on immune modulation of virus replication, or effects on local genital tract physiology.

Ulcerative and non-ulcerative STDs are cofactors for HIV transmission. Depo-Provera is known to alter cervical and vaginal epithelium in normal women (Valente *et al.*, 1998) which can become atrophic and develop post-partum like changes. Biopsies in Depo-Provera users has shown epithelial atrophy often associated with acute inflammation.

In a prospective observational cohort study on women prostitutes attending a STD clinic in Kenya, there was a strong association between HIV-1 infection and Depo-Provera use (Hazard ratio 2.2;95% CI, 1.4, 3.4) (Martin *et al.*, 1998). In a multivariate model controlling for demographic and exposure variables and biologic covariates, the adjusted HR for HIV-1 infection among Depo-Provera users was 2.0 (95% CI, 1.3,3.1).

The Population Crisis Committee (1992) recommends that women choosing to use injectable contraceptives who may be at risk of HIV infection should be counselled about using barrier method in combination with injectable contraceptives. However, the use of Depo-Provera has been found to discourage the use of condoms. In 536 women from 17 clinics in South eastern Texas who were using Depo-Provera as a contraceptive, the use of condoms for protection

against STDs was examined (Sangi-Haghpeykar *et al*, 1997). Among women who were using condoms prior to using Depo-Provera, nearly half said they never or rarely did so after starting on Depo-Provera. Only 18% used condoms consistently while using Depo-Provera. Factors associated with consistent condom use were, being Black (OR 2.0), being unmarried (OR 2.2), having a history of an STD infection (OR, 1.8), having previously used condoms (OR 2.7), and having no interest in future child bearing (OR 1.8).

The widespread use of Depo-Provera may in fact demotivate couples from using condoms. Depo-Provera may thus not be the contraceptive of choice in populations which are at a high risk for HIV infection.

Safety Aspects of Depo-Provera
II. Impact on the Health of the Progeny

11. Intrauterine exposure to Depo-Provera

"....congenital anomalies including female fetal masculinization and clitoral hypertrophy have been observed following larger doses of progestogens."

(Upjohn Co., 1984).

"....a significant increase in incidence of polysyndactyly and chromosomal anomalies was observed among infants of users of Depo-Provera, the former being more pronounced in women under 30 years of age."

(Upjohn Co., 1994).

Much of the information on the teratogenic effect due to *in utero* exposure has come from studies on hormonal pregnancy tests, hormones given as supportive therapy for habitual and threatened abortions, and oral contraceptives. One of the reasons for banning hormonal pregnancy tests (high fixed dose estrogen-progesterone combination drugs) worldwide was due to their association with congenital anomalies in fetus exposed to the drug *in utero*.

Depo-Provera is being offered as a temporary method of contraception for couples planning a birth interval of more than 2 years (WHO, 1990). Deep intramuscular injections of 150 mg Depo-Provera are recommended every 3 months, with the first injection being given during the first 5 days after the onset of normal menstrual period, within 5 days postpartum if not breast-feeding, and if breast-feeding, at the sixth week postpartum, to ensure that the contraceptive is not administered inadvertently to pregnant

women (Upjohn Co., 1993). Although the effective dose of Depo-Provera is considered to be for 90 days following a single injection of 150 mg, the active drug and its metabolites are detectable in the blood for as long as 200 days (Fotherby *et al.*, 1980). Pregnancies which follow discontinuation of Depo-Provera may result in the exposure of fetus to the drug *in utero* and, any potential teratogenic and mutagenic effects of the drug would be of serious concern. In addition, accidental pregnancies in women on Depo-Provera would also be subject to such risks.

The evidence for mutagenesis and teratogenesis could be in the form of increased rates in spontaneous abortions, malformations, and chromosomal anomalies.

Toxicological Information

In a review of toxicological information on Depo-Provera, Jordon (1994) has reported that in dogs, Depo-Provera can produce chromosomal aberrations in germ cells when administered intramuscularly at a dose of 5 mg every other day for several weeks and in hamsters when injected at a dose of 1-5 μg three times a week for several weeks. Medroxyprogesterone acetate has also been shown to increase the induction of sister chromosome exchange in rabbit lymphocytes and mouse kidney fibroblasts. However, primigravid C57B1/6J mice when treated with sub-dermal pellets delivering MPA in dosages of 5.0, 50.0, and 500.0 mg/kg/day on gestational days 7 through 19 did not show any non-genital malformations (Carbone *et al.*, 1990).

Administration of a long acting progesterone could lead to a high rate of spontaneous abortions. Nine baboons were injected with norethisterone in the form of a slow release intramuscular injection during early pregnancy (Beck *et al.*, 1982). Six of them aborted spontaneously between 27 and 35 days of pregnancy. The authors concluded that this observation provided a basis for suspecting that progestogens when administered continuously during pregnancy have an early abortifacient effect.

In vivo study on human fetus

Orally administered Medroxyprogesterone acetate (MPA) crosses the placental barrier and accumulates in the fetal adrenal glands. A total of 40 mg labelled MPA was administered orally to 4 pregnant women who were admitted for medical termination of pregnancy (Besch *et al.*, 1966)[24] . The control group comprised of 3 nonpregnant women with normal endocrine function who had been admitted for surgery for carcinoma cervix. Four male fetuses of 11, 12, 16 and 22 weeks were aborted by standard procedure. Samples of maternal, placental, and fetal tissues and fluid were collected for analysis of radioactivity. Both maternal and fetal tissues actively concentrated or accumulated MPA. The fetal adrenal to blood ratio was by far the greatest for any of the tissues or fluid studied. The gastrointestinal tract, kidney, lung, testis and brain showed a progressively increasing amount of label from the 11th to 22nd week.

Epidemiological study

The study cited in the current Upjohn drug literature, the only published epidemiological study on *in utero* exposure, is a hospital based study carried out between July 1975 and January 1978, in Chiang Mai, Thailand (Pardthaisong *et al.*, 1988). The results were published in 1988, four years after the Public Board of Inquiry set up by the USFDA had recommended that the approval as a contraceptive be delayed (Weisz *et al.*, 1984).

In this study, all births in McCormick hospital, Chiang Mai, in the 2 1/2 year period of observation were monitored. All live born and still born children were examined by a single pediatrician who was blind to the maternal medical and contraceptive history. The study population comprised of 4023 non-contraceptive users, 3312 women who had used oral pills and 1229 women who had used Depo-Provera prior to or during the index pregnancy.

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24. There is no information on whether informed consent was taken for this study. (Study funded by Upjohn Co., and United States Public Health Service).
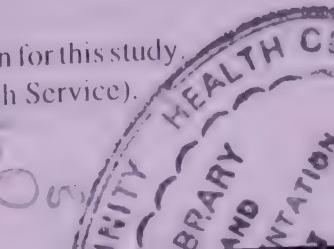
The relative risk of major defects for Depo-Provera users versus non-users and pill users were 1.70 and 2.9 respectively. The overall excess of major defects was due to the higher rates of limb defects and chromosomal anomalies. The limb defects were mostly confined to peripheral abnormalities such as polydactyly and syndactyly. The relative risk of polydactyly and syndactyly associated with Depo-Provera use was 4.8 as compared with non-use and was statistically significant ($p < 0.05$). Among women under the age of 30 years, the relative risk was 5.7 ($p < 0.01$).

In the peripheral limb defect, only two cases had a clear family history and both of these occurred in Depo-Provera users. If only the isolated cases of peripheral defects were taken, the rate in Depo users was 4.9/1000 births and that in non-contraceptors was 1.7/1000 births and the difference was not significant. However, if the rates were compared with pill users (1.29/1000), then it was significant at, $p < 0.05$ level.

The prevalence of chromosomal anomalies in Depo-Provera users was 4.1/1000 births (5/1229) and that in the non-contraceptors was 0.49/1000 births (2/4023)(The figures and rates in the original article are discrepant between the tables and new rates have been computed). Among women under 30 years of age, the relative risk of chromosomal anomalies in Depo-Provera users *vs* nonusers was, according to the original paper, 5.3. However, on recomputing, the relative risk is 11.0. Down syndrome was the most common chromosomal anomaly observed in this study; the incidence in non-contraceptors was 0.25/1000 and that in Depo-Provera users was 2.4/1000, a ten fold increase.

Of the 14 Depo-Provera users in this study who gave birth to a child with a limb defect and/or a chromosomal anomaly, only 4 were pregnant while using Depo-Provera, and the rest had conceived after the expected effect of the last dose (200 days).

From the exposure history, it would appear that only 4 Depo-Provera users who gave birth to a child with either a limb defect or chromosomal anomaly would have had their fetuses exposed directly to Depo-Provera when *in utero*. However, the major flaw in

the interpretation of this study has been to consider the peripheral limb defects as the manifestation of teratogenic effect of Depo-Provera and therefore "unrelated" to chromosomal anomalies.

Teratogenesis or mutagenesis

Certain categories of polydactyly and syndactyly cases such as polydactyly postaxial, polydactyly preaxial II, III, IV etc., are known sentinel markers for point mutations (McKusick, 1992) and can take place with a distant exposure to a mutagen, even when the exposure is as far back as childhood.

In this study, precise diagnostic criteria have not been applied for the polydactyly-syndactyly cases, and therefore it is difficult to categorize these cases as proven Mendelian disorders or those due to teratogenesis. Even with the current study, what is required is a precise classification of the polydactyly-syndactyly cases according to accepted international criteria of genetic disorders. On the basis of this, mutation rates in Depo-Provera users can be calculated.

The conclusion of the authors, that these two defects (limb defects and chromosomal anomalies) are "unrelated" is thus not valid. It is possible to postulate a biological mechanism to explain the high prevalence of these two disorders in Depo-Provera users. Since mutagenic effects can manifest themselves many years following exposure, the distant exposure does not preclude the possibility that some of the polydactyly and syndactyly cases are also an outcome of mutagenic changes in the germinal cells due to the use of Depo-Provera.

Misclassification of exposure is also another issue that needs looking into. In this study, exposure was defined differently for gravid and nulligravid women. For gravid women, only the pregnancy interval prior to the index pregnancy was considered for classification of use or non-use of contraception. In contrast, for nulligravid women contraceptive status was determined by ever or never use.

40% of the non-contraceptors in this study were parous. It is

possible that some of them may have used Depo-Provera in the earlier period also. It would be important that they too are reclassified as ever/never users. A reclassification of exposure may reveal a different exposure history in some of the polydactyly-syndactyly cases which are currently classified as unexposed.

The authors have stated that there is a need for further investigations in larger populations before causal associations are proven. While their statement is unexceptional and this study has some limitations in that it is hospital based, subject to selection bias, these findings suggestive of a mutagenic potential of Depo-Provera are serious enough to question its use as a spacing method in women in the reproductive age group.

The visible chromosomal anomalies are only the tip of an iceberg. Estimates have shown that about 15.5% of all conceptions recognized from the 5th week of gestation onwards do not survive till birth and the proportion of all recognised pregnancies associated with both embryonic and fetal deaths and a cytogenetic abnormality is 4.5% (Hook, 1982). Thus, roughly 30% of all embryonic and fetal deaths recognised after the 4th week of gestation are associated with a chromosomal anomaly.

The probability of pregnancy loss is greatest immediately after conception and falls steeply through the first trimester, with 90% of the spontaneous abortions occurring before the 11th week of gestation. The risk of spontaneous abortion is 14 times greater for fetuses with chromosomal anomalies than for fetuses without them (Buffler, 1982).

The increased rate of chromosomal anomalies at birth in Depo-Provera users could indicate that a higher proportion of pregnancies are being aborted spontaneously. However, in a population based study on pregnancy outcomes carried out in the same population in Chiang Mai, Pardthaisong and Gray (1991) did not find increased rates of spontaneous abortions in pregnancies exposed to Depo-Provera as compared with non-users. A possible explanation could be that the control group comprised of women from one of their earlier studies on return of fertility following discontinuation of

contraception (Pardthaisong *et al.*, 1980) and were thus not true never-contraceptors. The control group was different from the exposed group in that they were not exposed to Depo-Provera during the index pregnancy. This may have led to a dilution of difference, if any, between the two groups.

Ascertainment of early spontaneous abortions is extremely difficult in field conditions because a greater proportion of them are reported as delayed or missed period (as a prolongation of amenorrhoea or lengthened cycle). An occult abortion is defined as a pregnancy which aborts so soon after its implantation that its existence is not suspected except by a few days' delay in the onset of an otherwise normal menstrual period. The data of Block (1976) indicate that approximately 37.5% of those cycles which would otherwise have been thought to represent a prolonged luteal phase were actually occult abortions. This when seen in the context of secondary amenorrhoea and delay in return of fertility in Depo-Provera users who discontinue the contraceptive in order to conceive (Pardthaisong, 1984), could indicate that in these women a considerable proportion of conceptions are probably terminating as occult abortions.

The available information from both toxicological and the hospital based studies raises serious concern about the possibility of a mutagenic effect of Depo-Provera. In the light of this evidence, the use of Depo-Provera as a spacing method of contraception needs to be questioned.

Effect on birth weight

Depo-Provera has an adverse effect on the health and survival of children who are exposed to the drug *in utero*.

A cohort of 1573 pregnancies in women who were administered Depo-Provera during pregnancy (830 accidental pregnancies and 743 pregnant at the time of administration) were compared with a control group of 2578 women who had planned their pregnancies (Pardthaisong & Gray, 1991).

The proportion of women giving birth to low weight babies (2500 gms) was significantly higher among the Depo-Provera group

compared to the controls. This difference was seen regardless of whether the information on birth weight was obtained from medical records only or from a combination of records and maternal recall.

The odds ratio for low birth weight, adjusted for maternal age, birth order, maternal height, rural/urban residence, antenatal care, smoking during pregnancy, and place of birth was 1.5 (95% CI, 1.2, 1.9). The risk was also significantly elevated when analysis was restricted to parous women. The adjusted odds ratio for low birth weight infants was high irrespective of whether the exposure was accidental or the women were pregnant before the first use of Depo-Provera (OR 1.4 and 1.7 respectively). Infants conceived within 4 weeks of the injection had a significantly higher incidence of low birth weights than the infants who were conceived at later intervals. The test for trend was significant (x^2 for trend = 4.77; p = 0.009).

The authors of the study have put forward selection bias as an explanation for the adverse results. While this may be true for women who were pregnant before starting Depo-Provera (either because the woman came late for the injection, or the woman was not diagnosed at the time of injection, or the woman used the contraceptive as an abortifacient), this may not be a valid reason to explain the adverse effect seen in accidental pregnancies i.e., method failures, which formed a substantial proportion of the sample.

Effect on infant health

In infants exposed to Depo-Provera *in utero* the survival rate is also adversely affected. The cohort of infants born to women exposed to Depo-Provera during their pregnancy was followed up for their outcomes (Pardthaisong & Gray , 1991). Perinatal mortality rate was significantly raised in infants of Depo users in comparison with the infants born to the control group (55.9/1000 live births and 31.6/ 1000 live births, RR 1.8, p <0.001). A significant difference was seen in neonatal mortality rate as well (44.3/1000 and 19.8/1000 respectively, RR 2.2, p <0.01) .

The cause specific mortality rate due to prematurity and low birth

weight was significantly greater in the Depo-Provera group. The authors postulated that the low survival rate in infants exposed to Depo *in utero* was probably mediated through low birth weight which was in the causal pathway between exposure and outcome.

The excess risk of deaths were confined to the group of children exposed to Depo-Provera as a result of accidental pregnancy. The neonatal and infant mortality rates were higher for infants conceived within four weeks of Depo-Provera injections than for infants exposed at later post-injection intervals. The trend in declining mortality with longer injection to conception intervals was seen in this study also (neonatal mortality, x^2 for trend 14.66, p =0.0001; infant mortality x^2 for trend 7.48, p = 0.006).

The validity of these two studies on pregnancy outcomes and infant survival has been questioned on the following grounds: The pregnancies in the Depo group were "unwanted" whereas those in the control group had been planned; the estimation of dose to conceptus and timing of the injection was imprecise and subject to recall bias; that women on Depo gain 'weight' and pre-pregnancy weight and weight gain have not been included in the analysis, although their effect would have been in the opposite direction; and that contrary to the findings in this study progesterone is thought to prolong pregnancy leading to reduction in prematurity and low birth weight (Hogue, 1991).

In response, Gray and Pardthaisong (1991) have argued that the increased risk of low birth weight in pregnancies that were estimated to have occurred within one month of injection cannot be explained by selection bias because they were all contraceptive failures; and that the gestation age had been taken from records maintained by the Family Planning clinics of the hospital and had been recorded before the study was initiated, thereby eliminating observer bias and recall bias. Their final conclusion is " We cannot explain our findings which were contrary to our expectations and this led us to speculate that the results might reflect an association between peak maternal serum levels of medroxyprogesterone acetate and adverse effects on the embryo and fetus".

To the response made by Gray and Pardthaisong, we would like to add that an 'unplanned' pregnancy need not be synonymous with an 'unwanted' pregnancy. Contrary to western values, in third world countries, a birth of a child, albeit unplanned, is still not seen as a disaster. Moreover, in this study 2.6% of the women in the Depo group who really did not 'want' the child had terminated their pregnancies and this was statistically different from the control group (p<0.01).

Effect on puberty

The surviving children in the study (Pardthaisong & Gray, 1990a) were followed up till puberty (Pardthaisong *et al.*, 1992). A higher proportion of children with "any exposure to Depo-Provera during pregnancy" had a suboptimal growth in height (RR 1.2; 95% CI 1.0, 1.4; p < 0.05), but on adjusting for socio-economic variable, the difference between the two groups disappeared.

The mothers were asked about changes in voice, muscular development and pubic/axillary hair growth in their male children. There were no differences in males between the Depo-Provera group and controls in the proportion of boys who showed signs of pubertal development.

Among girls, up to age twelve, the proportion of girls who had experienced menarche or had evidence of breast development was somewhat lower in the Depo group compared to the control group but the difference was not significant (Mantel Haenszel test $x^2 = 2.37; 0.05<p<0.1$). In the older age groups, the proportions were not different. Among girls, there was a significant difference in the delay in appearance of pubic hair growth between the two groups in the study ($x^2 = 3.99$, p = 0.05, RR =0.61, 95% CI, 0.4, 1.0). Due to cultural sensitivities, the development of pubic hair was not observed directly, the investigators relying on reporting by mothers.

In the normal female, adrenarche precedes gonadarche (Blake, 1993). The appearance of pubic or axillary hair in the absence of other signs of puberty is called precocious puberarche (adrenarche). It is likely to be a result of increases in adrenal androgen. The delay

in reported appearance of pubic hair in girls exposed *in utero* to Depo-Provera may be an indication of decrease in adrenal andro-gen. An *in-vivo* study on human fetus cited earlier has shown the excessive accumulation of Depo-Provera in the fetal adrenal glands (Besch *et al.*, 1966).

One major limitation of this study is that the control group is not an unexposed population. They were different from the exposed group by not having had exposure to Depo-Provera during the index pregnancy. Many of them were probably ex-Depo users since this is the part of the world where Depo-provera has been widely available since the mid sixties. Classifying them as unexposed would make the exposed and control group similar thereby shifting the RR towards unity. Another limitation is that the inter-viewers relied on reporting by the mothers who may not have directly observed the bodily changes of their adolescent children of either sex.

This study has not examined the effects on intellectual and social development.

Changes in personality and intellectual development

Although the results of various studies are inconclusive or conflict-ing, prenatal exposure of human fetuses to synthetic progestin and oestrogen is reported to affect personality.

600 records from Los Angeles clinics and a private medical practice were reviewed (Reinisch, 1977). 34 families were identified in which at least one other pregnancy had been treated with synthetic hormone and at least one pregnancy had not been treated with these hormones. Final sample had 42 hormone-exposed children aged 5 to 17 years (15 males and 27 females) and 42 unexposed siblings aged 6 to 18 years (18 males and 24 females). The children were given age-appropriate Wechsler intelligence scale and Cattell per-sonality questionnaires. Confounding variables were controlled during analysis. On an average, the families belonged to high socio-economic status.

Prenatal hormone exposure significantly affected subjects' re-

sponses to the personality tests. The P_o group (high progestin intake with little or no oestrogen) was significantly different from the O_p group (high oestrogen and low progestin intake, ratio being 4:1) on five personality scores ($p \leq 0.05$). The P_o group was significantly more independent, sensitive, individualistic, self-assured and self-sufficient while the O_p group was more group oriented and group dependent. The P_o group was characterised as 'inner'- or 'self'-directed and the O_p group as 'outer'- or 'other'-directed. There was no alteration in the IQ scores.

Intrauterine exposure to progestins appears to increase aggression responses. 17 girls (age 6-17 years) and 8 boys (age 6-18 years) whose mothers were treated during the first trimester with synthetic progestins were evaluated on a measure designed to estimate the potential for aggressive behaviour (Reinisch, 1981). The control for each of the exposed children was a sibling of the same sex who had not been exposed to progestins. The progestins administered to mothers included 19 NET, ethynodiol, hydroxyprogesterone caproate and MPA. These hormones had been administered singly or in combination and the dose in boys ranged from 670 to 8790 mg and in girls from 590 to 6500 mg. Exposure to synthetic progestins during gestation appeared to have a significant effect on their responses to Leifer-Roberts Response Hierarchy. When exposed girls were compared to their unexposed sisters, their scores representing the number of times physical aggression was chosen were significantly higher ($p<0.01$). Exposed boys also had a higher score ($p<0.01$). There was no difference in the number of verbal aggression between the groups.

A group comprising of 15 girls with prenatal exposure to high levels of medroxyprogesterone acetate (mean dosage 1086 mg, in an average duration of 17.1 weeks) was compared with 15 girls with no hormonal exposure *in utero* (Ehrhardt *et al.*, 1977). The MPA girls were more frequently described as falling into categories of 'low" or "average" in physical expenditure and atheletic skills although the difference was not significant. There was a border line significant difference with respect to being labelled as a tomboy during childhood ($p=0.062$) and in the area of feminine clothing

(p=0.035). The MPA group showed less tomboyism and preferred more feminine clothing. MPA was considered to have an enhancing effect on female sexually dimorphic behaviour.

In a similar study, the effect of prenatal MPA was assessed in a group of 13 exposed boys with 13 unexposed boys (Meyer-Bahlburg *et al.*, 1977). There was no statistically significant difference between the groups in the areas of energy expenditure, athletic skills, sex of playmates, being teased for effeminacy or gender preference.

Ehrhardt and colleagues (1977) have concluded that the difference in findings between the boys and girls does not preclude the possibility of an effect of MPA on the central nervous system. Two explanations have been put forward: one is that the male fetus is exposed to much higher levels of androgens produced by his own testis which overcomes the antagonising effects of MPA; the other is that in males, cultural factors strongly counteract subtle tendencies to deviate from the norm.

170 teenagers exposed *in utero* to MPA or Depo-Provera were compared with a group of 817 controls (Jaffe *et al.*, 1988). Among boys there was a delay in some milestones as reported by the mothers. Mothers of exposed boys more often reported their offspring to have talked single words late, talked sentences late, and walked late. Verbal and spatial ability tests did not reveal any intellectual impairment. On testing for aggression responses, on Buss-Durkee overall aggression scale, there was no difference between the exposed and control group. However, mothers of exposed boys more often reported that their offspring were noted to be more "naughty" in school compared to the control group (23.6% and 12.5% respectively).

The above study was on a retrospective cohort of women who had antenatal interviews conducted between 1965-68. The study was double blind in that the testers were unaware of exposure status and both the subjects and the testers were unaware of the hypothesis being tested. These children and their mothers were

traced in 1985-86 and 8.6% of the original cohort formed the study sample. The study does not report the percentage of non-response either due to no trace or refusal to participate in the study.

Potential for accidental exposure *in utero*

While the many adverse outcomes in pregnancies exposed to Depo-Provera have not been disputed by Upjohn Co. they seem to take comfort by emphasising that Depo-Provera should be given within the first five days after the onset of normal menstrual period, within five days postpartum if not breast feeding and if breast feeding, then within 6 weeks of delivery (Upjohn Co., 1993). This would hypo-thetically prevent accidental exposure of the fetus to Depo-Provera. The reality may be quite different.

Indian women are more likely to ovulate before the effective duration of Depo-Provera is over. In a comparative trial carried out in a group of Indian women and Swedish women, it was found that all the women in the Indian group ovulated within 73 days of injection of Depo-Provera (Fotherby *et al.*, 1980). The ovulation occurred before the duration of effective dose was over (90 days) and when the drug level in the blood was above 0.6 ng/ml. This could mean that there is a considerable chance of high method failure rate in Indian women.

In the multinational WHO study on use effectiveness, failure to return for an injection within a specified period was the most important cause for disco..tinuation in the non-medical category (WHO, 1977).

In the three-year study period on *in utero* exposure to Depo-Provera and pregnancy outcome (Pardthaisong & Gray, 1991), the investi-gators were able to recruit 1573 women who had been exposed *in utero* either accidentally or after they had conceived. This indicates that under field situations, a large number of pregnancies will be exposed to Depo-Provera.

Under field conditions, it is more than likely that a large number of women will be administered Depo-Provera even if they come later

in their menstrual cycle especially since the window of time for injection is so small[25] .

The currently available pregnancy tests are not sensitive enough to detect conception before a period is missed and hence ruling out a pregnancy during this period is not possible. As the study carried out in Thailand has shown, the pregnancy rate among women who received Depo-Provera between the 9th and 28th days of their cycle was as high as 6.2/100 women (Liskin & Quillin,1983). Moreover when a woman comes for a repeat injection, amenorrhoea due to Depo-Provera may mask the amenorrhoea due to pregnancy and she may be subjected to more than one dose before her pregnancy is detected (See section on effectivenes).

The attributable risk of adverse effects of exposure to Depo-Provera during pregnancy will be much higher when the contraceptive is marketed due to its unacceptably low use effectiveness. And as the study from Thailand has shown, a considerable proportion of women might use Depo-Provera in the mistaken notion of it being an abortifacient (Pardthaisong & Gray, 1991).

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25. A woman with normal bleeding days of 3 will probably come for her first injection after the bleeding days are over which gives her barely two days.

12. Exposure of the infant through breast milk

"Warnings

Lactation

Detectable amounts of drug have been identified in the milk of mothers receiving Depo-Provera. In nursing mothers treated with Depo-Provera contraceptive injection, milk composition, quality and amount are not adversely affected. Infants exposed to medroxyprogesterone from breast milk have been studied for developmental and behavioral effects through puberty. No adverse effects have been noted."

(Upjohn Co., 1993)

Effect of Depo-Provera on the composition of breast milk

The growth and development of infants could be affected if Depo-Provera changes the composition or volume of breast milk. Unlike the combined oral contraceptives, Depo-Provera does not appear to reduce the volume of milk in breast feeding women (Schwallie, 1981; WHO, 1984)). One uncontrolled study showed a significant increase in milk volume (Karim *et al.*, 1971). Depo-Provera is, however, known to have serious effects on the composition of the breast milk.

A comparative study carried out on women from three centres in two countries has shown that Depo-Provera has an adverse effect on the lipid concentration in breast milk (WHO Special Programme, 1986). A controlled double blind clinical trial was carried out in Hungary and Thailand to examine the effects of oral contraceptives on milk lipid and its fatty acid content. The control group were

women using no contraception or barrier mathods. In the two Thai centres women using Depo-Provera formed an additional group for comparison.

In the group from Thailand who were given Depo-Provera, a reduction in the proportion of total milk lipid occurred at the first two visits (9 weeks and 12 weeks) after administration of the injection. Compared to baseline values, there was a fall in lipid content by 11% and 15% and compared to corresponding controls, the fall was 16% ($p<0.05$) and 29% (<0.001) respectively.

The reduction in milk fat occurred in both the progestin only contraceptive and the Depo-Provera group suggesting that this effect was an effect of progesterone analogues. There was a reduction in the proportion of palmitic acid content with Depo-Provera ($p<0.01$). This effect was seen to a lesser degree with progestin only contraceptive, indicating that progestin analogues reduce milk fat synthesis. The linoleic acid (an essential fatty acid) exhibited an increase with Depo-Provera at 9 weeks. However, the amounts of linoleic acid in gms/L of milk showed that there was actually less in Depo-Provera milks in comparison with corresponding controls at 9 and 12 weeks. This has raised the concern that the reduction in essential fatty acids in the milk of women on Depo-Provera could mean that the delivery of other fat soluble nutrients through breast milk could also be affected.

The women in this study, even those from Thailand were selected on the basis of their nutritional status. Their babies were born with a birth weight of more than 2700 gms, and the women were well nourished and in apparent good health. Despite this, there was a fall in the fat content of breast milk.

With regard to undernourished women who were not represented in this study, the investigators concluded that " under marginal nutritional conditions, the milk lipid level would be expected to be lower. In those developing countries where the habitual diet is low in fat, there would be a greater dependence on fat synthesis for milk production and potentially a greater susceptibility to a drug which suppresses fat synthesis. It would be prudent to investigate the use

of these contraceptive steroids in mothers who are less well nour-
ished than those involved in this study or where it was considered
that they or their infants might be at risk of under nourishment"
(WHO Special Programme, 1986).

Essential fatty acids are necessary for growth, development of the
reproductive and immune systems. In human milk, the lipid content
accounts for about 60% of the dietary energy which may be of
special importance in growing infants during illness or periods of
food shortage. A contraceptive that adversely affects the composi-
tion of breast milk in such an important way should be contraindicated
in a population where breast milk is very often the only available
food for an infant.

There are conflicting reports about the effect of Depo-Provera on
the protein content of milk. One study has reported that Depo-
Provera affects the protein content of breast milk by up to 16%
(Ratner, 1981). Another study comparing women receiving inject-
able contraceptive (Depo-Provera or NET-EN) during lactation
with a control group showed a statistically significant ($p<0.05$)
decrease in protein content in most of the groups including the
control group (Karim et al., 1971). This was, however, considered
to be a reflection of the low protein diet of the population.

Transfer of Depo-Provera through the breast milk

Depo-Provera is excreted through the breast milk of the lactating
woman. In 7 lactating women after an injection of 150 mg Depo-
Provera, Depo-Provera levels in breast milk were similar to plasma;
the ratio being almost 1:1 throughout the study period of upto 87
days (Saxena et al., 1977).

A study carried out in Thailand showed that in 8 of 10 women
administered Depo-Provera, there were detectable levels of the
drug in both milk and serum 12 weeks after injection (Koetsawang
et al., 1982). The ratio of milk serum concentration of Depo-
Provera varied from 0.12 to 2.60 (mean 0.88). On the assumption
that an infant ingests 600 ml milk daily, the investigators have
calculated that the daily intake of steroids in the first week after

injection would be 1 to 13 μg. By eight weeks, the amount of Depo-Provera in the milk would still be considerable and twelve weeks after the injection, the amounts of Depo in human milk could still be as high as 1 μg /day. In addition to the maximum amount of the contraceptive in the milk, it is also important to consider the total amount ingested on a particular occasion.

The 150 mg of Depo-Provera given three monthly to a woman is regarded as an equivalent of 1.8 mg/day dose to the woman[26] . On this assumption, it has been estimated that a suckling infant would ingest on average 2.1 % and at maximum 27.7% of the weight adjusted maternal daily dose (Benett, 1988). It has been argued that while an infant may ingest between 0.08 and 0.25 μg/kg/day of Depo-Provera through breast milk, the amount of progesterone ingested through cow's milk is far higher at 1.5 to 6 μg/kg/day (Emery, 1993).

Medroxyprogesterone acetate (MPA) is well absorbed from the gastrointestinal tract (Dollery, 1991) and food appears to enhance its absorption. Following ingestion, peak drug levels are seen within 2 to 6 hours. With daily oral dose steady-state conditions are achieved within 2 to 3 weeks. MPA crosses blood brain barrier and accumulates in liver and kidneys. MPA is extensively metabolised in the liver. One of the major metabolites of MPA is a glucuronide. Depo-Provera itself has a glucocorticoid effect.

Animal studies

The effect of ingestion of Depo-Provera through breast milk has been seen in experimental animals. The study was carried out on 28 control and 32 experimental female young and 19 control and 19 experimental male young of rats the Charles Foster strain (Satayasthit et al., 1976). The mothers of the experimental young were given 5 μg MPA/g body weight intramuscularly on day 3 of parturition. There was no difference in growth rates in the experimental and control group. However, female experimental young showed a significant delay in the onset of vaginal opening ($p<0.05$),

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26. The calculation is 150 mg / 12 x 7 days.

in the initiation of the first oestrous cycles in the young (p<0.01) and a difference in body weight on day of vaginal opening (p<0.05).

In another study, (Logothetopoulos *et al.*, 1961) three male and three female albino rats of Wistar strain were injected with 6 alpha-methyl-17 alpha hydroxyprogesterone acetate (Provera) from the first postnatal days to maturity. There was no difference between the treated animals and their controls of either sex until the age of 50 days. Treated and control females maintained the same growth curves. However, in the treated male group, the increase in body weight seen at puberty was absent. A very significant difference in body weight was established at 65 days. The adrenal glands of the treated animals reached only 1/6 of the weight of the control groups. On morphological criteria, Provera seemed to produce a complete inhibition of the secretion of gonadotrophins and corticotrophin by the pituitary. The degree of atrophy and the histologic changes in the adrenal glands and in the gonads were similar to those reported late after hypophysectomy. The recovery of these glands were extremely slow after the cessation of the injections.

Effect on breast-fed infants

Depo-Provera is recommended for breast feeding women after 6 weeks post partum in order to 'protect' the infant.

Breast-fed infants of 55 women initiating Depo-Provera contraception 42 days after delivery and 51 receiving it from the 7th day postpartum onwards were compared with 100 women followed up from the 7th postpartum day as controls (Karim *et al.*, 1971). After the third month, there was a significant increase in the milk volume which continued till 6 months postpartum (p<0.01) in Depo-Provera infants. The weights of the exposed infants also increased significantly after the third postpartum month (p<0.01). The study did not control for any confounding variables.

In a retrospective clinic-based study (Jimenez *et al.*, 1984), children exposed to Depo-Provera through breast milk were followed up when they were approximately 4 1/2 years old and compared with a non-exposed group of controls. From the original cohort, 74% of

the exposed children (n=128) and 71.7% of the controls (n=142) formed the final sample. There were no differences in the height, weight, or rate of illness between the two groups. The findings regarding the rate of illness seems somewhat questionable because of recall bias. For instance, the mean incidence of diarrhoeal episodes reported by the mothers during the first 12 months was almost 40 to 50% less in both the exposed and control group as compared with that reported for the general population in the same area.

A more recent prospective non-randomised multicentre clinic-based study carried out by the WHO, investigated the effects of progestin only contraceptives (oral and injectables) on growth, development, and health of infants exposed during lactation from 6 weeks postpartum (WHO, 1994a). Among the 2466 mother-infant pairs, 541 had received Depo-Provera and 876 were in the non hormonal methods group (IUD or sterilization). The Depo-Provera pairs were from Assiut (n=116), Chiang Mai (n=119), Khon Kaen (n=112), and Nairobi (n=194). The discontinuation rate ranged from 5% in Chiang Mai to 44% in Nairobi. The women were well nourished with mean values for height, weight and haemoglobin within the normal range. Only in Assuit, the haemoglobin level was less than 12 gms. In the Depo-Provera group, significantly higher proportion of women from Assiut (40%, p<0.001) and Nairobi (65%, p<0.01) belonged to "low" standard of living[27].

Overall there were no difference in weight change in infants between the exposed and the control group. Assiut was the only centre where the increase in weight for infants at three months in the Depo-Provera group was significantly higher (p<0.001) as compared to the non-hormonal controls. This was reflected in the rate of change in arm circumference also, with Assiut being the only centre with a significant increase at 3 month (p<0.001), at 6 months and 1 year (p<0.05). In the skinfold thickness measurements, the Depo-Provera group in Chiang Mai had a smaller decrease at 12 months than the infants in the other group.

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27. Standard of living not comparable between countries.

One of the limitation of these studies assessing effect of exposure through breast milk on the health of the children is the use of weight as an important parameter. Considering that Depo-Provera and some of its metabolites have glucocorticoid-like effects, weight may not be the most appropriate measure of health in the exposed children. In order to rule out glucocorticoid-like effect on children exposed through breast milk, a simultaneous measurement of levels of cortisol in urine and serum would be necessary.

In a small study 13 women (6 from Thailand and 7 from Kenya) with full term healthy male infants received Depo-Provera on days 42+1 and 126+1 post partum days. Infants of 9 women who did not receive Depo-Provera served as controls. Blood samples were collected from exposed women on days 44,47,74,124,128, and 130 postpartum days for measuring the level of medroxyprogesterone acetate. Four hour urine was obtained from all the 22 infants in the morning on days 38, 40, 42, 44, 46, 53, 60, 67, 74, 88, 102, 116, 122, 124, 128, 130 and 137 days. Urinary FSH, LH, unconjugated testosterone and unconjugated cortisol were measured by radio immuno assay and serum and urinary MPA metabolites were measured. No MPA metabolites could be detected in the urine of the infants of exposed mothers. There were no differences in testosterone or cortisol levels. However the decline of the unconjugated testosterone, LH and FSH showed a steeper decline in the controls as compared with the exposed infants (unpaired t test $p < 0.05$).

The same sample of infants from the previous WHO study (1994a) were administered 19 types of development tests (WHO,1994b). The results were conflicting and no consistent pattern was seen. When the Depo-Provera group was compared with the IUD group (control group), the results varied between centres. In Khon Kaen, three significant differences were observed in which the mean age for passing the test was earlier in Depo-Provera babies. In Assuit, of the six significant differences, only one test was passed later by the Depo-Provera babies. In Chiang Mai, of the seven significant differences, in six tests, the Depo-Provera babies passed the tests at a later age than their controls. In Nairobi, the results were biased

because of the 44% drop out rate by three month. The results are not comparable among the centres because of cultural differences.

A long-term follow-up of children breast-fed by mothers on Depo-Provera has examined effects on the height and weight of children (Pardthaisong et al., 1992). Children exposed to Depo-Provera only through breast milk were not different from the control group. Children exposed to Depo-Provera during lactation and pregnancy showed a significant decrease in height (RR 1.4; 95% CI, 1.2, 1.8; p < 0.01). There was an increased risk in children with a history of 'any exposure to Depo during lactation'[28] (RR 1.2; 95% CI 1.0, 1.3; p <0.05). However, when these estimates were controlled for socio-economic variables, the differences between the two groups disappeared[29]

The study has not reported findings, if any, on the development of signs of puberty in these children. This is a little surprising because the same study has presented results of the effect of exposure to Depo in utero on the appearance of signs of puberty.

Although not included in the labelling, Depo-Provera is administered to children with precocious puberty (WHO, 1982; Liskin & Quillin, 1983).

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28. This group comprised of children exposed in utero and lactation plus children exposed through lactation only.
29. This study has been cited in the section on exposure in utero and is subject to the same critique.

13. Discussion

Depo-Provera is being promoted as a safe contraceptive by the pharmaceutical Upjohn Company, research scientists and a section of the medical community. To demonstrate safety Depo-Provera must meet certain critieria which relate to its nature as a chemical entering the body and to its function as a contraceptive. As a chemical entering the body safety requirements for approval are the same as that for the other drugs used in therapy; as a contraceptive a few additional requirements of safety need to met.

Drugs in clinical practice are administered to 'diseased' persons for therapeutic purposes and they act by altering/modifying/changing/ or correcting an abnormal pathological process in the body. In contrast, contraceptive drugs are to be used by normal healthy women and they act by interfering with normal physiological mechanisms of ovulation and conception, converting them into 'abnormal' processes. In case of temporary methods of contraception, these abnormal processes should reverse once the method is discontinued and the ability to conceive and to bring to term a normal, healthy child should not be tampered with irreversibly.

As drugs used exclusively by women in the reproductive age group, the risks of administering a contraceptive to women during this period of their lives need to be weighed against the possibility of the drug's effects on progeny either *in utero* or through breast milk.

Apart from the possibility of teratogenic and mutagenic effects, with steroidal hormonal contraceptives an additional area of concern is their effects on the reproductive health of the progeny. These delayed effects may manifest at the initiation of puberty, the onset

of endogenous hormone production, and continue for part or the whole of the reproductive period[30].

Depending on the potential number of users, computation of risks and benefits is different at the population level as well. From the public health point of view, it is important to assess the potential number of individuals who could develop an adverse drug reaction (ADR[31]) as a consequence of using a particular drug.

Targeted at all sexually active persons for the duration of their reproductive life, contraceptives are administered during the most productive healthy years of the adult part of life. For women, it is approximately from the age of 15 to 45 years of life[32]. In India, the number of women who are considered "unprotected", and therefore, in need of contraceptives are estimated to be 41.08 millions (GOI, 1999). When used by such a large population, even a small risk of adverse effect can assume great public health importance as the absolute numbers manifesting the adverse effects will be very large.

Depo-Provera is licensed for use in inoperable cancer and for contraception. Depo-Provera in high doses of 400 mg to 1000 mg per week followed by a maintenance dose of 400 mg per month is used as an adjunctive, palliative therapy in inoperable, recurrent, metastatic endometrial and renal carcinoma. The high risks posed

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30. The most infamous being the example of development of clear cell adenocarcinoma in young women exposed *in utero* to a synthetic estrogen, diethyl stilbesterol.

31. The USFDA terms all harmful reactions associated with a given drug as *Adverse Drug Experiences*. These include those occurring during as well as subsequent to the administration of a particular drug. Adverse experiences definitely shown to be caused by a drug are termed *Adverse Drug Reactions*. The term *Serious* Drug reactions are reserved for those reactions which are definitely harmful to the person and/or possibly life-threatening (Martin, 1978).

32. In reality, the contraceptive drugs may not be ingested throughout the reproductive life of 30 years. In India, Depo-Provera ia being promoted as a temporary method for spacing children. In a 'typical' situation, the duration of use could extend upto 10 years of age with breaks in between for pregnancy.

by a hazardous drug would be acceptable if its use in inoperable cancer increases the probability of survival. These same risks may assume a different magnitude if the drug is to be recommended for contraception even in a much smaller dose.

Depo-Provera is a long-term, systemic, invasive contraceptive, acting at multiple levels. Its potent efficacy and ease of use have been cited as two reasons for its promotion in populations with high birth rates and low 'motivation' levels. However, under 'field' conditions, as the section on efficacy has shown, the 'typical' effectiveness may not match up to its effectiveness projected from clinical trials.

According to the Upjohn Co., experience with Depo-Provera has been accruing since the mid sixties. Yet, the published literature on the safety aspects of this drug is scanty and does not reflect forty years of research. The available studies suffer from inappropriate study designs, inadequate sample size, lack of appropriate comparison groups, and high dropout rates or loss to follow-up. Results are selectively presented and the conclusions are often reached after an inadequate analysis without controlling for confounding variables. The studies carried out by renowned research bodies are also not exempt from several of these short comings.

Reporting of cases and case series is important in alerting the medical community to ADRs with the use of a particular drug. Research on association of thromboembolic phenomenon with combined oral contraceptives was set off by the publication in 1961 of a single case of pulmonary embolism in a 40 year old premenopausal woman using oral contraceptive preparation to treat endometriosis (Jordan, 1961).

Case reports indicating adverse clinical outcomes with Depo-Provera is virtually absent from literature despite widespread use (Westhoff, 1996). This has been stated as evidence for lack of ADRs and evidence for the alleged safety of the drug (Liskin & Quillin, 1983). At the same time, these reviewers also point out that since most of the long-term users are in developing countries, cases are less likely to be reported.

There could be other reasons as well. Many of the manifestations of the ADRs with Depo-Provera would result in the affected woman seeking medical help from practitioners other than a gynecologist. For instance, a woman with stress fracture due to Depo-Provera, if she has access to appropriate medical care will be directed to an orthopedic surgeon[33] . If the surgeon is not aware of Depo-Provera and its association with bone loss because the published medical literature underplays and minimizes the risk, s/he is unlikely to ask the relevant question regarding exposure.

Published studies appear to reflect the preoccupation of the research scientists rather than that of the several million woman-months of experience. When a woman reports a symptom while on Depo-Provera, the general tendency and advice seems to be to "reassure" her that the reported symptom is not associated with the contraceptive use. By not taking the woman's experience in using the contraceptive seriously, it is more than likely that important morbidites are being missed out. Thus we have reports on *discontinuation* due to bleeding disorders but not on the *incidence* of bleeding disorders and more than thirty years pass before the need to assess its effects on haemoglobin and ferritin levels becomes an important area for research[34] .

Even with all these limitations, the picture that emerges from the review is that in both women and her progeny, Depo-Provera causes serious adverse drug reactions which could lead to life-threatening complications or life-long disabilities.

Deaths have been reported following the use of Depo-Provera as a contraceptive. In the multinational comparative clinical trial of Depo-provera (n=1587) and NET-EN (n=1585) carried out by the WHO, of the four women who were reported to have died during the course of the study, two of them had received Depo-Provera (WHO, 1983). One woman, aged 28, had completed chemotherapy

33. This in any case is an unlikely scenario for poor people living any where in the world.
34. The first study to look at these effects was published in 1998. For a critique of this study see p 34-36.

(methotrexate) for a hydatidiform mole four months prior to the admission to the study. She received two injections of Depo-Provera for contraception and two months later was hospitalised for metastatic choriocarcinoma. She died approximately two weeks later. The second death in the Depo-Provera group occurred after a two-week period of generalised illness including fever, cough, and malaise. The woman, aged 22, was hospitalized for a day, though no abnormalities were noted on physical examination. According to her family, she became unconscious on the way home from the hospital and died the following day of "undetermined" cause. She had received three injections of Depo-Provera. No autopsies were performed on the women who died[35].

In the trial carried out by the Fertility Research and Biostatistics Division of the Upjohn Co., recruiting 3,857 women for a total of 72,215 women months of experience with 150 mg Depo-Provera three monthly, one woman is reported to have developed fatal pulmonary embolus associated with disseminated carcinoma of the lung (Schwallie & Assenzo, 1973)[36].

Depo-provera increases the risk of atherogenesis and cardiovascular disease. There has been one reported case of intercranial hypertension and one report of fatal stroke in an Asian woman, a smoker who had received two injections of Depo-Provera (Liskin & Quillin, 1983). The same reviewers report that among 11,500 women using Depo-Provera over 200,000 woman-months, 15 women (1.3 per 1000) developed blood clots or thromboembolic disease.

Oral contraceptives containing estrogen are also associated with thromboembolic phenomena. But with the injectables the problem is compounded because the drug once injected cannot be withdrawn

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35. The other two deaths in the NET-EN group were due to miliary tuberculosis and "suspected" tuberculosis. All the four deaths were in women recruited from developing countries. The report goes on to say that "Four deaths over a period of two years is not surprising among more than 3,000 women living primarily in developing countries" (WHO, 1983). Thus, does a research organization of the caliber of WHO explain deaths during a *clinical trial*.

36. In this study, 4 women developed deep vein thromophlebitis of the lower extremities and one developed right subclavian vein thrombosis. The report does not reveal the eventual fate of these women.

from the body. Hence, if thrombosis develops in the first week of the administration of Depo-Provera, the adverse reaction is likely to progress, perhaps to a fatal outcome, because of the continued presence of the drug in the body for the next three months or more. The practice of prescribing estrogens to control the bleeding disorders, which apart from being a treatment of dubious value, will add to the cardiovascular risks of Depo-provera[37].

The findings of the study showing the increased shedding of HIV-1 infected cells in cervical and vaginal secretions in Depo-Provera users is a new area for concern. Use of Depo-Provera could become an important factor in the vertical sexual transmission of HIV. The inflammatory effect of Depo-Provera on the cervical mucosa, which is one of its mechanism of contraceptive action, may increase transmission of HIV from males to females as well.

Ectopic pregnancies, increase in the risk of breast cancer, cervical cancer including carcinoma *in situ*, in subgroups of women are other life-threatening risks with Depo-provera.

Depo-provera causes serious adverse reactions which could lead to life long disability. In women, the risk of osteoporosis and the lifetime risk of fracture is increased.

Return of fertility is delayed and in subgroups of women it may lead to permanent infertility due to irreversible atrophy and fibrosis of the ovaries.

By virtue of its hypoestrogenic effect, Depo-provera converts the body of a young woman in the peak of her active life into that of a premenopausal woman. The woman experiences a fall in the quality of life due to the complete disruption of her menstrual cycle and the several "side effects" ranging from fatigue to loss of libido.

Infants exposed to Depo-Provera *in utero* have an increased perinatal and neonatal mortality risks. The most serious adverse effect of *in utero* exposure appears to be the mutagenic effect of Depo-provera and the increased risk of giving birth to children with chromosomal anomalies including Down's Syndrome.

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37. Estrogen-progestin combination injectables are the new generation injectables currently being tested in third world countries.

Depo-Provera affects birth weight adversely. Fat composition of the breast milk is altered and this could have a serious effect on breast-fed infants from developing countries. The increased weight in breast-fed infants of Depo-Provera users reported in studies could very well be the manifestation of the glucocorticoid effect of the drug.

The weight of evidence relating to the hazardous nature of Depo-Provera is sufficient to compel its proponents to admit to the injectable's potential for adverse outcomes including death. However, the issue is side-stepped and the relatively high maternal mortality in developing countries is cited as reasons for differing risk-benefit assessment for use in developed and not so-developed countries (WHO, 1982; Chilvers, 1994).

While it is debatable whether high contraceptive prevalence alone as a single measure will reduce mortality and morbidity posed by pregnancy related causes, in the context of the third world countries. three points need to be remembered. Firstly, the population at risk of pregnancy may be different from the population at risk of contraception; secondly, the contraceptive risks may be an added on risk to pregnancy risks; and thirdly, the very factors that are responsible for the high obstetric deaths in a developing country would increase deaths due to Depo-Provera use[38].

The review of literature presented in this monograph is to enable the reader to weigh the risks and benefits of the use of Depo-Provera as a temporary method of contraception in women from the disadvantaged sections of society.

Depo Provera appears to be hazardous to the health of the woman and her progeny. The contraceptive appears to be not suitable for nulliparous women, adolescents, breast feeding women, women who have not completed their family, and women who are in the reproductive age group. In short, there does not seem to be a single group of women for whom Depo-Provera can be safely recommended as a contraceptive method of choice.

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38. These pertain to the nutritional status and medical care available to the majority of the population.

Afterword

"I am saying, let it (Depo-Provera) be available. Nobody is forcing anybody to take it. Let the doctor decide what is right for the patient. Obviously, the doctor will monitor its use and if there are problems, no doctor or patient is foolish enough to continue its use.

Why should it be banned, and why should we have to smuggle it for our patients? Who are these women protesting against it? Illinformed, so-called feminists, who are just a bunch of college girls with nothing better to do. Without going into the issue they are making a noise about it. Barging into meetings, carrying placards, shouting slogans. There are so many more important issues that need attention. Why don't they do something about slum children dying or about the blind?

They say that the first world is trying to foist it on the third world women. This is rubbish. A lot of life-saving drug came to us after being formulated and tested in the West, they didn't object to those, but here they have a platform to make a lot of noise and hulla-baloo about nothing. What kind of ethics are these? For at least the next decade there won't be a perfect contraceptive. Every drug has some side-effects. It is up to the doctor and the patient to decide what is best method. My only concern is for my patients.

Depo-Provera has been available all over the world for years, it has been used in Sri Lanka, Napal, Pakistan, Bangladesh for over two decades. Why should only Indian women be deprived of its use? They say that the precautions will not be properly implemented. If some doctors are careless, penalise them, why ban the drug? Don't Indian women need contraceptives? The injectable contraceptives has the same hormones as the oral pill. If the pill can be used, why not the injectables? I think there should be cafeteria approach. A

wide range of options—pill, IUDs, injectables—should be made available and the doctor should be able to decide which one is suitable for which patient. Why do these women seek to destroy the patient-doctor relationship?

Calling for a ban on Depo-Provera is like the anti-abortion protests, which want to take away the choice from women. I have come across so many cases of women who publicly opposed abortions, but quietly went and had abortions done. I am sure a lot of women who are opposing Depo-Provera will take the injections themselves. It is alright to be clever when it comes to other people. They have no right to dictate to responsible doctors what they should or should not prescribe to their patients. If there are a few black sheep, pick on them, don't deprive everybody else of the use of a particular drug, especially when all research has proved these contraceptives to be safe.

There is no suitable male contraceptive yet, and a lot of men don't want to use condoms. The wife bears the brunt of repeated and unwanted pregnancies. It affects her health and quality of life. I am in favour of women being given a control over contraception and the size of their families."

R.P. Soonawalla

Eminent gynaecologist, Bombay.
Principal Investigator, Post Marketing Surveillance Study, Depo-Provera.
(Interview, *Hindustan Times*, May 22, 1994: 10).

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Annexure I.
Approval of Depo-Provera

In the USA:

In 1960, Depo-Provera was initially approved by the United States Food and Drug Administration (USFDA) for treatment of endometrial and renal cancers, endometriosis, and for preventing spontaneous abortions. Later in 1971, approval for use in threatened abortion was withdrawn because studies did not support efficacy of Depo-Provera in preventing abortions. Moreover, progestogens given in early uterine life were known to cause congenital malformations.

In 1967, Upjohn applied to the USFDA for approval for use as a contraceptive. Approval was not granted despite the unanimous recommendation of the USFDA's Obstetric and Gynaecology committee. This was because of the adverse findings from toxicological studies carried out on animals which raised the possibility of breast and endometrial cancers in Depo users.

In 1981, a special panel of experts was appointed by the USFDA to scrutinise both toxicological and epidemiological data on the carcinogenic potential of Depo-Provera. The panellists concluded that the animal studies had been poorly designed and the epidemiological data was too haphazard and uncoordinated to assess long term risks (Sun, 1984). In 1984, following a five day public hearing, the Public Board of Inquiry recommended that Depo-Provera should not be approved for contraceptive use in the USA.

The non approval by the USFDA meant that the Upjohn Co. could not market Depo-Provera as a contraceptive in the USA. It also meant that the United States Agency for International Development (USAID) could not distribute the contraceptive as part of the AID programme in third world countries. Some countries like India also refused to approve the contraceptive in their national FP programmes.

In 1991, the final results of a multinational case-control study on the risk of breast cancer with Depo-Provera was published. The results

showed an apparent lack of an association. Following the publication of these results, the USFDA invited Upjohn to submit a 'new drug application'. In Oct 1992, the USFDA approved Depo-Provera as a contraceptive.

In India, clinical trials with Depo-Provera had been initiated by the ICMR in the seventies. However, in 1975, the unacceptably high rates of bleeding disorders in the women who were given Depo-Provera (ICMR, 1975) together with the adverse ruling by the USFDA led to the suspension of these trials.

In June 1993, because of the approval granted by the USFDA, the Drugs Controller of India granted a 'no objection' to the Upjohn Co. to market Depo-Provera in the private sector. In November 1993, the Indian company, Max Pharma was given approval to import and market the contraceptive in India.

Annexure II
Legal Requirements for the marketing of a new drug

In India, till 1987, there was no regulation on clinical trials. In June 1987, following the filing of a public interest litigation in the Supreme Court[39], the Government of India through an extraordinary Gazette notification expressed its intention to amend the Drugs and Cosmetics Act, 1940. This notification was confirmed in Sept 1988, and rules relating to clinical trials were incorporated into the Drugs and Cosmetics Act as Schedule Y.

According to Schedule Y, (Requirement and Guidelines on Clinical Trials for Import and Manufacture of New Drug),

> *"The clinical trials required to be carried out in the country before a new drug is approved for marketing depend on the status of the drug in other countries. If the drug is already approved/marketed, phase III trials as required under item 7 of Appendix I usually are required".*

Since Depo-Provera is already approved/marketed in the USA the country of the parent company, the drug has to go through Phase III of clinical trials. Item 7 of Appendix I is on confirmatory trials (phase III).

> *" The purpose of these trials is to obtain sufficient evidence about the efficacy and safety of the drug in a larger number of patients generally in comparison with a standard drug or a placebo. These trials may be carried out by clinicians in the concerned therapeutic areas, having facilities appropriate to the protocol. If the drug is already approved/marketed in other countries, Phase III data should generally be obtained on at least 100 patients distributed over 3-4 centres primarily to confirm the efficacy and safety of the drug in Indian patients when used as recommended in the product monograph for the claims made".*

Depo-Provera has not gone through the mandatory Phase III clinical trials in India. Apart from the legal necessity, Phase III trials are needed because of pharmacodynamic reasons[40].

Instead, the Drugs Controller of India has made post marketing

surveillance (PMS) conditional to the marketing of Depo-Provera. Thus, PMS is being made to substitute Phase III trials. Moreover, according to the guidelines in Schedule Y, the sample size of 100 patients distributed over 3-4 centres seem arbitrary and without any epidemiological basis.

Legal liability

The Drugs Controller of India, Dr P Dasgupta when asked about legal liability stated that he was not liable but he had taken on "conscience" liability (Anandani & Sathyamala, 1995a). He further stated that his powers did not extend to enforcing liability on the Upjohn Company.

On the other hand, the Upjohn Company representative in India, Mr Sunil Seghal, stated that one of the reasons for the high price of Depo-Provera in the USA was due to liability (Anandani & Sathyamala, 1995b). In the USA both the doctor who prescribes it and the company that produces the product are liable. However, he did not feel that liability would be a problem in India.

According to the Drugs Controller of India, under the New Economic Policy, any doctor can import and test any drug on Indian women. It appears as though India is also set to follow on the footsteps of Thailand as far as clinical trials and contraceptives are concerned.

The Upjohn Company had conducted its initial trials in Chiang Mai, Thailand, through the McCormick hospital. Chiang Mai is a remote rural area in Thailand and as the studies in this monograph have shown, it has been the 'testing ground' for Depo-Provera. Being rural, and non-literate, the women in these studies would not have been informed that they were taking part in clinical trials and no protection, legal or otherwise would have been made available to them.

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39. The PIL was against the introduction of NET-EN into the Family Planning programme in India. The case, Stree Shakti Sangatna and Ors vs Union of India, was filed in 1986 and continues to pend before the Supreme Court.

40. For instance, in a comparative pilot study carried out on Indian and Swedish women, all the women from India ovulated within 73 days of a single dose of Depo-Provera. In contrast, none of the Swedish women ovulated until more than 156 days after injection (Fotherby et al., 1980). The multinational comparative clinical trials with Depo-Provera and NET-EN had to be prematurely terminated because of the very high failure rate in an Indian centre, Chandigarh (WHO, 1977).
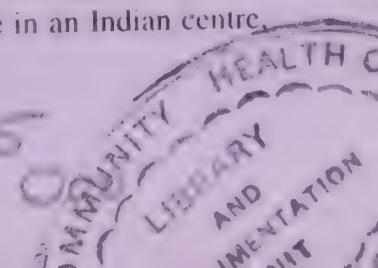
Annexure III
Improving Contraceptive Choices in the National Family Welfare Programme

An executive summary of proceedings of the workshop held in Mumbai on December 17-18, 1998 at Professor R.D.Cloksi Auditorium, Tata Memorial Hospital, Parel, Mumbai-400012.

Convened by : Institute for Research in Reproduction, Mumbai.
Supported by : Ministry of Health & Family Welfare, Government of India, New Delhi; WHO, SEARO (New Delhi); and CONRAD Programme.

The prime objective of the Workshop was to review the status of available injectable contraceptives in the adjoining Asian countries *vis-a-vis* that in India and to debate the pros and cons of their induction or otherwise in the National Family Welfare Programme. With this objective in mind, scientists from countries such as China, Thailand, Indonesia, Bangladesh, Sri Lanka, Nepal, Pakistan and Bhutan, where injectables Depo-Provera (DMPA) and NET-EN are available in their respective National Family Welfare Programmes, were invited to share their views and clinical experience. The scientists from Nepal, Pakistan and Bhutan were unable to participate.

The Indian Council of Medical Research is a nodal agency that conducts clinical trials with contraceptives before being inducted in the National Family Welfare Programme. The Council had generated considerable data on DMPA and NET-EN in mid 1970s and early 1980s. Injectable contraceptives are available in the Indian market since 1994. Scientists from ICMR and Clinicians with experience in the use of injectable contraceptives in their clinical practice were requested to share clinical experience and views at the workshop. Upjohn Pharmacia and Schering-AG, The two major pharmaceutical firms who are marketing Depo-Provera and NET-EN, respectively in the Indian market since 1994, were asked to share data on post-market surveillance and product-sale. Representatives from WHO, SEARO, the World Bank, UNFPA, USAID, the Population Council, Non-Governmental Organizations like

FPAI and several women's health groups were also invited to share their views and experiences and discuss issues related to injectable contraceptives. Agencies involved in social marketing of injectables were also invited. The whole exercise was to initiate a dialogue between different groups, and if feasible, to recommend to Government of India certain actions for follow up.

The views that emerged during the meeting were. (Specific)

- injectable contraceptives have been used as a method of contraception by more than 12 million women on over 100.countries.

- Progestin-only injectables Depo-Provera (DMPA) and Noristerat (NET-EN) are effective contraceptives when given every 3 months or 2 months, respectively.

- There are approximately nine million Depo-Provera users and one million NET-EN users.

- Progestin plus an estrogen, combination contraceptives are used as monthly injectables.

- Monthly injectable combination contraceptives in use are:
  The Chinese injectable number 1: Used by approx. 1 million women.
  Perlutal (Topasal, Perlutan) : Used by approx. 1 million women.
  Cyclofem and Mesigyna : Phase 3 and Introductory clinical trials.

- Information available on monthly injectables was limited and was not enough to draw reasonable conclusions in relation to the national needs.

- Progestin-only injectable contraceptives are highly effective and are comparable in effectiveness to voluntary sterilization (i.e., less than 1 pregnancy per 100 women).

- The contraceptive effect of injectable contraceptive is reversible, In fact, after two years the pregnancy rates among former Depo-Provera, NET-EN, IUD and OC users are the same,

- The safety, including long-term side effects, of an injectable contraceptive use has been demonstrated since its first use in 1961. No adverse effects have been noted on blood pressure, blood coagulation, breast feeding, liver function, cancer, foetal and child development.

- Besides effective contraception there are other possible additional benefits in injectable contraceptives.

- Progestin-only injectables may help women with certain medical conditions in addition to preventing unwanted pregnancies. These include prevention of endometrial and ovarian cancers, reducing anaemias, prevention of pelvic inflammatory disease, epilepsy and endometriosis.

- As with all other contraceptives, there are some side effects with the use of injectable contraceptives. Major reason for discontinuation being disruption of regular menstrual bleeding and the induction of amenorrhoea. Heavy profuse bleeding has also been reported in some cases with injectables Depo-Provera and NET-EN. These side effects are reversible.

- Amenorrhoea has been perceived both in a positive as well as negative way by different communities in different cultural settings accepted by some and the method has been discontinued by others. Those with positive attitudes have accepted the method while those with negative attitudes have discontinued it.

- The importance of counselling and appropriate medical intervention was evident in the better acceptance of the method leading to higher continuation rates in most cultural settings. Without counselling, the continuation rate was low with both NET-EN and DMPA.

- As with other contraceptive there are also some known contraindications for the use of injectables. These include pregnancy, unexplained vaginal bleeding and current breast cancers. For other relative contraindications, benefits far out weigh the risks of repeated pregnancies, abortions, low birth weight babies and high maternal morbidity and mortality presently prevalent in most cultural settings.

- For a national programme, the cost and continued availability of the contraceptives were important. As with any other contraceptives, maximising access and quality of services had demonstrated better acceptance.

- There was the need for continued post-introduction/market sur-

veillance for recording very long term side effects in the national context.

- It was advisable, though not contra-indicated, not to use injectable contraceptives in adolescent and nulliparous women.

- A majority of the delegates were of the opinion that the progestin-only injectable contraceptives should be inducted in National Family Welfare programme.

A section of delegates, the Women's Health Groups, however strongly voiced their dissent to recommending any injectable contraceptives in the National Family Welfare Programme.

Recommendations

(1) Taking into consideration the available infrastructure at Primary Health Centres; the need for counselling; screening and appropriate back-up for medical interventions; injectable contraceptives should preferably be introduced selectively in suitably equipped centres and hospitals. It is stressed that the introduction should be gradual with emphasis on good clinical practice and rigorous post-introduction surveillance of the side-effects and patient-care.

(2) In the Indian context, studies need to be continued to find:
- What is the prevalence of menstrual irregularities in women not using any contraceptive (Control group)?
- What are the women's perception of amenorrhoea?
- What is the effect of induced amenorrhoea on the behaviour, osteoporosis and the onset of menopause?
- Are injectable contraceptive immuno-suppressive?
- Data should be available on the comparative trail of injectables with oral contraceptive pills.
- There is a need for study on the long-term effects of injectable contraceptives in the Indian-context.

Submitted by,

Dr. Sabita Tejuja   **Dr. H.S. Juneja**

(Chair Persons, Recommendation and Concluding Session, Workshop on "Improving Contraceptive Choices in the National Family Welfare Programme")

medico friend circle

Perspective

The medico friend circle (MFC) is a group of socially conscious individuals interested in the health problems of our people. MFC is trying to critically analyse the existing health care system which is highly medicalized and to evolve an appropriate approach towards developing a system of health care which is humane and which can meet the needs of the vast majority of the population in our country. MFC is trying to build a nation-wide current committed to this philosophy.

The existing system of health care, we have realized, is not geared towards the needs of the majority of the people, the poor. It requires a fundamental change. Such a change would occur as a part of the total social system in the country, since medical system is only a part of the total social system. MFC believes that the potential created by modern medical science cannot be realized fully without a fundamental change in the social system.

MFC thus tries to foster among medicos a current for upholding of human values and aims at restructuring the medical profession to enable it to realize the potential created by modern scientific medicine.

MFC offers a forum for dialogue/debate, sharing of experiences with the aim of realizing the goal outlined above and for taking up issues of common concern for action.

Activities

MFC members are spread all over India and they try to propagate the perspective of MFC through their work. Some members are engaged full-time in organising health projects in rural areas and

urban slums. Last year, MFC celebrated the twenty-fifth year of its existence.

Bulletin

MFC is as of today mainly a thought-current and the monthly (currently, bimonthly) *medico friend circle bulletin* now in its twenty-fifth year of publication, is the medium through which we communicate our ideas and experiences. The bulletin publishes articles broadly reflecting the MFC perspective on health problems. Publishing the MFC bulletin is our chief common activity. The bulletin is also read by a larger circle than its members through a subscription system.

MFC members gather once a year at an all India annual meet to explore a relevant topic through discussion or to understand the functioning of a particular health care project in terms of a chosen topic.

Study and action projects by local groups, regional camps to understand a local health problem and its broader dimensions and health educational campaigns are the other activities through which MFC has grown and consolidated. Some examples are: a camp on lathyrism in Rewa disctrict (MP), a campaign against oestrogen-progesterone forte; campaign about diarrhoea and misuse of drugs; and a campaign with women's groups against introduction of long acting injectable contraceptives.

In response to requests from groups working in Bhopal following the gas disaster, MFC intervened as a group (i) to study the health problems of the disaster victims; (ii) to support the efforts of voluntary groups and the emerging people's movements in an attempt to get rational health care for the affected people.

An epidemiological study (March' 85) followed by a pregnancy outcome survey (Sept' 85) were two such interventions. Technical support was given for health activities of many voluntary agencies and action groups working among the disaster victims.

Rational Drug Policy Cell

Concretely criticizing irrationalities in the production and use of drugs, and putting forward alternatives has been one of the activities of MFC members. MFC has therefore been an active part of the coming together of various drug interested groups from different part of the country to form the All India Drug Action Network (AIDAN). The movement towards a rational drug policy has been one of the rare example of different groups coming together on a health issue and preparing a substantial critique of the National Health Policy in India and an equally solid, concrete, alternative to it. MFC members have contributed to this movement by participating in seminars, newspaper campaigns, lobbying with the government and to the formulation of the perspective of AIDAN.

A Rational Drug Policy Cell has been formed to look after MFC's involvement in this issue. Two studies, evaluating the rationality of the top-selling antidiarrhoeals and analgesic formulations in the market have been published by this cell. These studies have been valuable in drug-campaigns and have been reprinted by KSSP.

Membership

Anyone who broadly agrees with the perspective as well as the rules and regulations of MFC is welcome to become a member. For more details, contact the convenor's office.

Forum for Women's Health

Forum for Women's Health is an autonomous women's organisation involved in action and networking on issues regarding contraception, reproductive technologies and genetic engineering as well as population policies. The activities started in November 1986 with a campaign against misuse of sex-determination and sex pre-selection techniques and consequent abortions of female foetuses.

The nature of the organisation then was that of a campaign group and it functioned as "Forum Against Sex-Determination and Sex Pre-selection". Through the campaign the close link of sex-determination and pre-selection with discrimination against women in general was highlighted. This campaign created an awareness regarding abuse of progress in the fields of science and technology to perpetrate violence against women. This led to efforts to understand the progress of science and technology from women's point of view. It also forced an examination of the links between health issues and issues related to contraception, population policies and reproductive technologies. Over the period of time the area of work has been expanded to cover all the aspects of larger issue of women and health. Hence the modification of the name.

In India, over the last few years the thrust of population control is on long-acting, provider-controlled contraceptives for women. The newer and newer contraceptives that have been developed over the years have all acted to take the control of fertility away from women. Further, only women are held responsible for contraception. Thus mere increase in the choice of contraceptives with a cafeteria approach has had no significant impact in terms of improvement of man-woman relationships which mainly remain unequal and vio-

lent. The Forum, hence, does not support any contraceptive which brings about systemic changes in the body—be it that of a woman or a man. The Forum asserts the distinction between birth control and population control. Birth control is control of fertility which is achieved by voluntary efforts of the partners whereas population control is a top-down, demographically driven philosophy and practice which channelises biological reproduction and sets and creates terms and conditions for motherhood. The activities of the Forum also include dissemination of information in English and regional languages and organisation of meetings and workshops on issues related to women and health.

About the author

Dr. C. Sathyamala is an epidemiologist trained at the London School of hygiene and Tropical Medicine, UK. Since the early eighties, she has been active in both the Health and Women's movement. In 1983, she coordinated the first successful all India drug campaign against the Hormonal pregnancy tests. She is one of the main architects of the technical case against the other injectable contraceptive NET-EN which is still pending in the Supreme Court of India. As part of the mfc initiative and as an independent researcher, she has coordinated two population based epidemiological studies on the people exposed to the toxic gases from the factory of Union Carbide Corporation at Bhopal in December 1984. She has co-authored a book on the political economy of health for field workers. A long-term member of the medico friend cricle, she is currently the editor of the organization's bimonthly journal. She continues to work in the belief that epidemiology can be a powerful tool in strengthening people's struggles.

Medico Friend Circle

Publications

In Search of Diagnosis. Ashwin Patel (ed). pp 175, 1977 (reprinted 1985).

Health Care: Which Way to Go: Examination of Issues and Alternatives. Abhay Bang and Ashwin Patel (eds). pp 256, 1982 (reprinted 1985).

Under the Lens: Health and Medicine. Kamala Jayarao and Ashwin Patel (eds). pp 326, 1986.

Medical Education Re-Examined. Dhruv Mankad (ed). pp 214, paperback Rs 35, hardcover Rs 100.

Bhopal Disaster Aftermath: An Epidemiological and Sociomedical Study. pp 76, 1985.

Distorted Lives; Women's Reproductive Health and Bhopal Disaster. October 1990, Rs 10.

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Cheques/money orders, to be sent in favour of Medico Friend Circle, directed to Manisha Gupte, 11 Archana Apts., 163 Solapur Road, Hadapsar, Pune-411028. Please add Rs. 10/- for outstation cheques.

Depo-Provera is being promoted as a safe contraceptive by the pharmaceutical Upjohn Co., research scientists and a section of the medical community. To demonstrate safety, Depo-Provera must meet certain criteria which relate to its nature as a chemical and to its function as a contraceptive. As a chemical entering the body, safety requirements for approval are the same as that for the other drugs used in therapy; as a contraceptive, a few additional requirements of safety need to be met.

Depo-Provera has recently been introduced into the Indian market. Yet, protests by women's, health, and consumer groups have prevented its introduction into the national family welfare programme. In India, unlike in the West, the carcinogenic potential of Depo-Provera, although an important consideration, is not the central argument to oppose its introduction as a contraceptive. In the Indian context, there are in fact more serious limitations that would also apply to women in other developing countries, as well as to low income and disadvantaged women from developed countries.

The approval by the Indian Drugs Control Authority is linked to licensing by the USFDA in 1992. With the approval of the USFDA, it appears as though the last word has been said on the safety of Depo-Provera as a contraceptive. The review of literature presented in this monograph is to enable the reader to weigh the risks and benefits of the use of Depo-Provera as a temporary method of contraception.

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